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INFLUENCE OF MINOR DIETARY CHANGES ON FREQUENCY OF INFANTS' STOOLS

STUDY OF THE EFFECT OF VARYING THE CONTENT OF LACTOSE, MILK FAT AND THIAMINE

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AND
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PHILADELPHIA

The clinical study here reported was designed to ascertain whether or not and to what extent certain small variations in the lactose, milk fat and thiamine content of a standard complete modified milk mixture for infant feeding are reflected in the stools when the protein and calories are maintained at constant levels. Such observations have wide application to the whole broad problem of artificial feeding of infants, inasmuch as lactose, milk fat and thiamine are significant ingredients of most feeding mixtures prescribed by pediatricians.

The preparation used[1] is an evaporated, homogenized, sterilized modified milk mixture prepared from whole milk, skim milk, lactose, vitamin B_1 (thiamine), iron citrate and concentrate of vitamins A and D from cod liver oil. It has been described by Eley.[2] After dilution with an equal volume of water the approximate composition is:

	Per Cent		Per Cent
Milk fat	2.8	Total milk minerals	0.6
Lactose	7.4	Calcium	0.11
Milk protein	2.8	Phosphorus	0.08
Water	86.4	Iron	0.0008

One fluidounce (30 cc.) provides 20 calories. Each reconstituted quart (0.95 liter) contains 2,500 U. S. P. units of vitamin A, 85 U. S. P. units of thiamine (vitamin B_1), 2 mg. of riboflavin (666 Sherman-Bourquin units of vitamin G, or B_2), 400 U. S. P. units of vitamin D and 8 mg. of iron. The vitamin C content is variable; additional amounts must be supplied from other prescribed sources.

Three variants of this basic modified milk mixture without alterations in caloric value or in protein content were subjected to clinical trial. In one variant (no. 1) the concentration of lactose was increased 0.8 per cent and the milk fat content decreased 0.4 per cent; the second (no. 2) was identical with no. 1 except that 1.6 per cent corn syrup replaced an equal amount of lactose, and the third (no. 3) was identical with no. 1 except that thiamine was not added, the amount of this vitamin thereby being reduced by about 40 per cent. These three preparations were compared with the reconstituted milk mixture (no. 4) as control. All four milk

The clinical studies from the Pediatric Clinic of the University of Pennsylvania Hospital herein reported were made under a grant from The Borden Company, New York.

1. This milk mixture is Biolac, manufactured by the Borden Company.
2. Eley, R. C.: J. Pediat. **19**:470, 1941.

mixtures were prepared from the same batches of fresh milk. The sole compositional differences are shown in the following tabulation:

Modified Milk Mixture, No.	Lactose, %	Corn Syrup, %	Milk Fat, %	Thiamine, U.S.P. Units
1	8.2	0.0	2.4	65-85
2	6.6	1.6	2.4	65-85
3	8.2	0.0	2.4	35-55
4	7.4	0.0	2.8	65-85

CLINICAL MATERIAL AND PROCEDURE

As experimental subjects a group of 249 normal newborn infants was collected over a period of one year, the infants being distributed into approximately equal groups (table) as they became available. The numbers of subjects of the two sexes were about equal, and Negro children predominated. Their ages at the start of the study ranged from birth to 8 weeks, the average for each group being between 4.5 and 5.2 weeks. The majority of the children were placed directly on the test modified milk mixtures when weaned from the breast, although a few whose mothers still gave them some breast milk were given the experimental formulas as complementary feedings for a period. Most of the babies remained under observation until 9 to 11 months of age.

The infants were kept in their own homes, under the guidance of a visiting nurse, who maintained close rapport with the mothers by weekly visits. Cooperation was excellent. Instructions called for mixing the contents of a can of concentrated milk (16 fluidounces [0.47 liters]) with 16 fluidounces of cool boiled water as directed by the physician. Medical supervision was

Distribution of Infants According to Sex and Color

Modified Milk Mixture	Male	Female	White	Negro	Total
No. 1	33	32	23	42	65
No. 2	32	26	27	31	58
No. 3	29	29	16	42	58
No. 4	33	35	32	36	68

carried out at a special feeding clinic, to which the infants were brought every two to three weeks during the first four months of life and at intervals of three to four weeks thereafter. All examinations were made by one physician according to a uniform set of procedures.

The first feeding was prescribed on the basis of 50 calories per pound (0.5 Kg.) of expected body weight, the intake being adjusted as growth and appetite warranted. The vitamin C requirements were met by the use of ascorbic acid tablets, 25 to 50 mg. daily. No vitamin A or D was given apart from that already present in the milk. Cereal was added at the twentieth week, puréed vegetables at the twenty-fourth week and fruits at the twenty-eighth week. Between the seventh and the ninth month egg yolk, potato, cottage cheese and milk desserts were permitted.

Generally speaking, the stools from all four formulas were closely similar, being yellow, soft and unformed. Although data originally were desired on the character of the stools as well as on their frequency, the subjective element inherent in the uncontrollable factor that mothers recorded the descriptions made those observations unreliable. The records of frequency, however, were considered dependably accurate; they showed little variation in rate from day to day for any individual baby.

Troublesome regurgitation or vomiting occurred rarely. Constipation, as evidenced by hard bowel movements or less than one evacuation per twenty-four hours, was similarly uncommon; when encountered it was intermittent, of short duration and easily corrected by giving prune juice in small amounts. Occasional temporary attacks of diarrhea were recorded, manifested by the sudden appearance of watery green stools mixed with mucus in association with an

increase in frequency. Such episodes were not usually accompanied by fever or other tangible evidence of infection. The therapy routinely employed consisted of diluting the feeding to half strength with boiled water; with older infants the usual solid foods were discontinued temporarily and scraped raw apple was substituted. No babies had to be changed from the experimental modified milk mixtures because of persistent gastrointestinal symptoms.

RESULTS

The average number of stools per day for each of the four groups was charted both in terms of the number of daily stools with the respective types of feedings for the first thirty days (chart 1) and in relation to the age of the subjects (chart 2). The first values were computed in order to detect any transient disturbance in intestinal function which might take place when the infants were changed suddenly

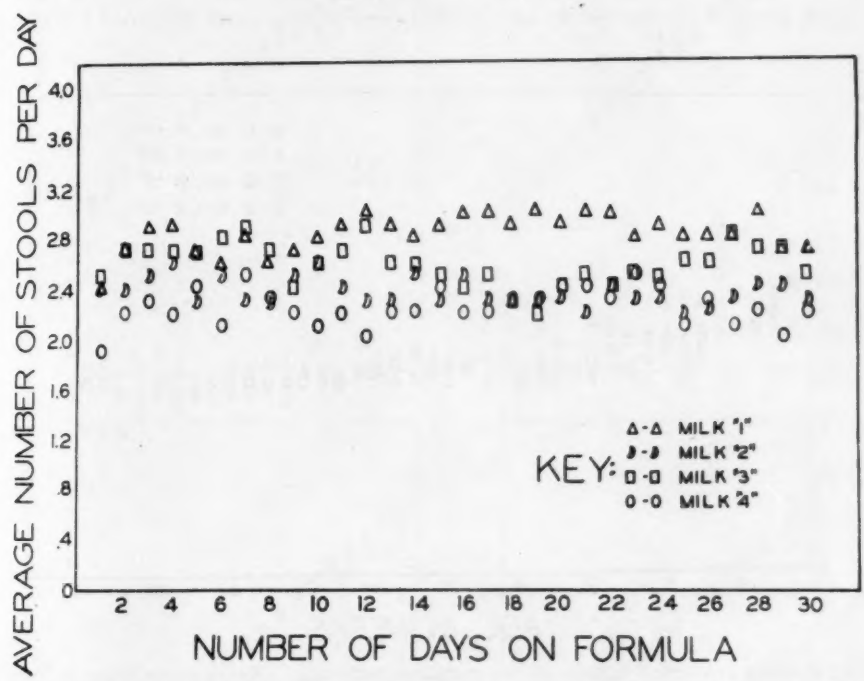

Chart 1.—The average number of daily stools plotted against the number of days since the feeding of the four special modified milk mixtures was begun without regard to the ages of the infants. Differences in stool frequency are clearly indicated.

from their former feedings to the new modified milk mixtures. The data (chart 1) show a distinct level of stool performance for each group of infants during the first month of the feeding trials. The following comparative judgments were made: Infants receiving formula 1, containing more lactose and less milk fat than the standard reconstituted milk mixture, had a frequency ranging from 2.6 to 3.0 stools per day. Those fed formula 2, also containing less milk fat and more carbohydrate, but with 1.6 per cent corn syrup in place of an equivalent amount of lactose, exhibited lower averages, with a range of 2.2 to 2.6 stools per day. Those fed formula 3, identical in carbohydrate and milk fat composition with formula 1 but with a decreased content of thiamine, had a frequency ranging from 2.2 to 2.9 stools per day. The group receiving formula 4 (the standard reconstituted milk mixture), containing 7.4 per cent lactose, 2.8 per cent milk fat and about 85 U. S. P.

units of vitamin B_1, had the least number of bowel movements, with an average of from 1.9 to 2.5 per day. The variations in frequency for the individual infants were least with formula 4.

In chart 2, relating the age of the patients to the average number of daily stools, similar relationships are perceived, though the differences in the results among modified milk mixtures 2, 3 and 4 were but slight. Mixture 1 was distinguished by the highest level of stool activity, with values elevated above the others.

That the infants grew equally well with all four modified milk mixtures is demonstrated by the composite growth curves for weight and length (chart 3). No instance of malnutrition or eczema was encountered in any of the groups. In order to check for the development of subclinical rickets or scurvy, roentgenograms of the long bones were taken every two to three months on 5 infants selected at random from each group. No evidences of rickets, even of the most minimal kind, were

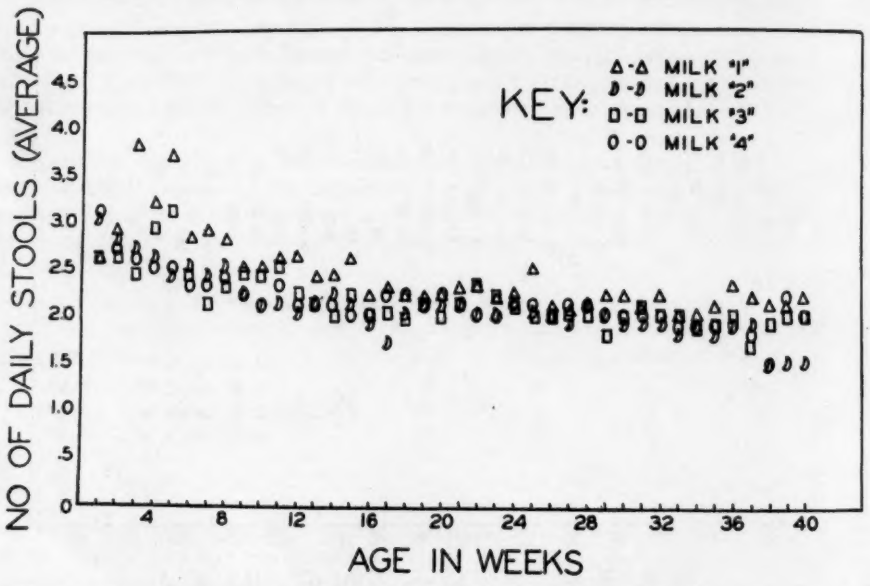

Chart 2.—The frequency of daily stools compared with age. Observations began at the time the infants were first changed to the test milk mixtures.

recognized, although 1 infant having otherwise normal bones roentgenologically presented persistent periosteal thickenings of each humerus. Two instances of scurvy were encountered: A boy who had received supposedly 25 mg. of ascorbic acid daily showed mild scorbutic lesions for the first time in the roentgenogram taken at 9 months of age. The other child when 40 weeks old suddenly presented the characteristic clinical and laboratory signs of frank scurvy, with hemorrhagic phenomena, a vitamin C level of 0.1 mg. per hundred cubic mentimeters of blood and pronounced roentgenologic changes. This boy was convalescent from pertussis; he had been receiving 25 mg. of ascorbic acid daily dissolved in the feeding mixture, but there had been much regurgitation and vomiting of feedings during paroxyms of coughing. Both infants recovered promptly with a high intake of vitamin C. After these 2 instances of vitamin C deficiency were discovered, the daily intake of ascorbic acid was raised from 25 to 50 mg. for all babies in the study groups.

COMMENT

It appears from the results that the average stool frequency of infants receiving a well balanced modified milk mixture [2] can be increased somewhat during the first few months of life by any of three minor compositional changes: (1) increas-

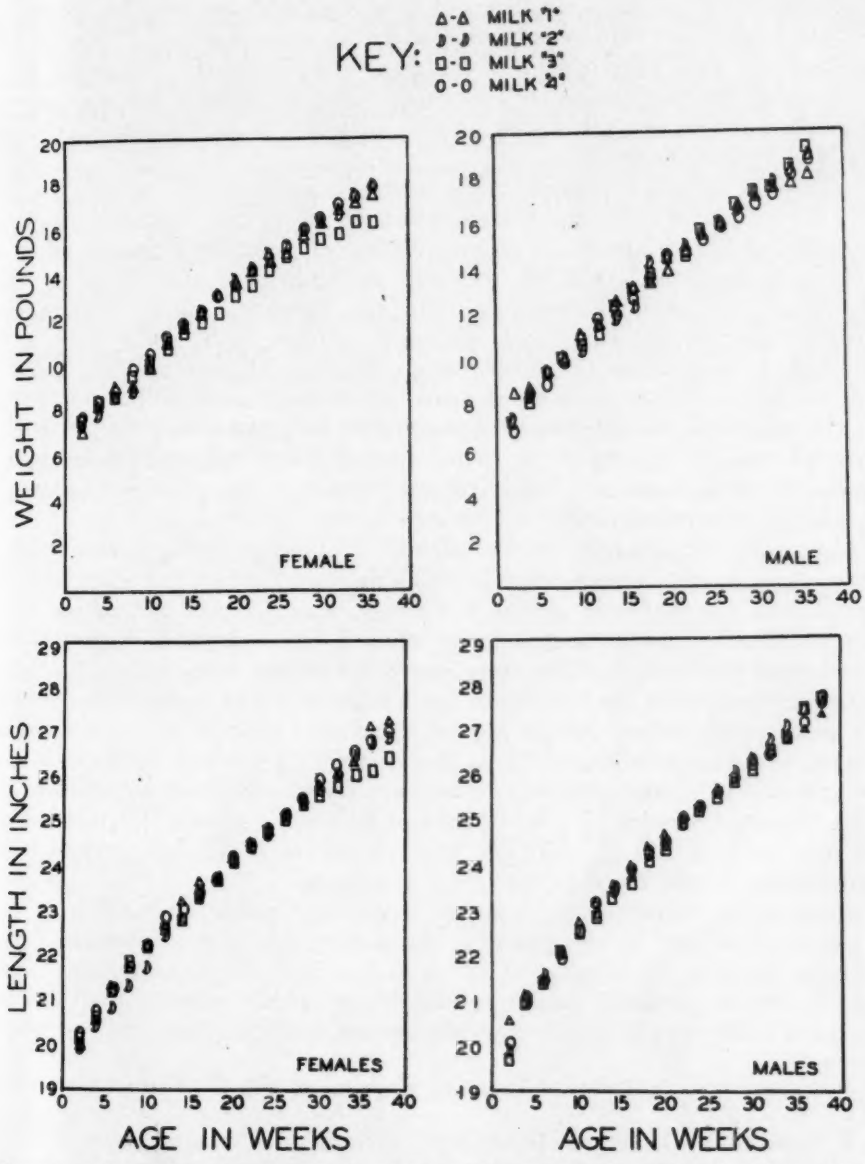

Chart 3.—Mean curves for growth in weight and length of male and female infants receiving the four modified milk mixtures. The various groups of curves coincide almost exactly.

ing the lactose content from 7.4 per cent to 8.2 per cent and decreasing the milk fat content in isocaloric amount; (2) decreasing the milk fat and increasing the carbohydrate content as in modification 1 but substituting 1.6 per cent corn syrup for an equal quantity of lactose (8.2 per cent total carbohydrate), or (3) decreasing the milk fat and increasing the carbohydrate content as in modification 1 but omitting

supplementary thiamine, the content of this vitamin thereby being reduced from a level of 65 to 85 U. S. P. units to 35 to 55 U. S. P. units. Stool frequency was highest with change 1, second highest with change 3 and was highest with change 2. The infants given the standard milk mixture had the lowest frequency of all groups.

Generalizations on stool frequency of these children after they had reached the twentieth week of age cannot be made safely, since extraneous solid foods in inconstant amounts were introduced into the dietary at that time. The prime purpose of continuing the observations until they were about 40 weeks of age was to uncover possible differences associated with growth, of which none was found. All babies grew and thrived normally.

Lactose in excessive amounts has a positive laxative action, as has been noted clinically for years.[3] The explanation seems to lie in the relatively low rate of absorption of lactose and its hydrolytic derivative galactose from the upper part of the intestinal tract,[4] with the resulting discharge of appreciable quantities of unassimilated lactose and galactose into the large intestine. The ready fermentation of these sugars by the lactic acid–producnig bacteria of the colon helps to form characteristic soft, semisolid stools, which pass quickly through the colon and rectum. The level of lactose in the standard reconstituted milk mixture was the same as for human milk, and the stool frequency was no greater than that recorded for breast-fed infants.[5] Raising of the lactose content would thus seem to be the factor responsible for the increase in stool frequency shown by the groups of infants given the modified milk mixtures with 8.2 per cent lactose.

A possible explanation for the slightly diminished average stool frequency shown by the infants receiving modified milk mixture 3, which had a lower thiamine unitage than the otherwise similar mixture 1, with 8.2 per cent lactose and 2.4 per cent milk fat, may lie in their being affected with a slight B_1 hypovitaminosis. An adequate intake of thiamine is necessary for proper tonus and motor function of the gastrointestinal tract, whereas lack of thiamine can result in hypomotility.[6] The needs of the infant, though not yet established exactly, have been estimated as being at a minimum level of 10 units of vitamin B_1 for each hundred calories of food consumed.[7] This quota was supplied by the standard control mixture no. 4, which contained about 2.7 U. S. P. units of thiamine (vitamin B_1) per fluidounce (30 cc.), or 13 U. S. P. units per hundred calories. No other evidence of B_1 hypovitaminosis was noted in the group of infants.

Discovery of roentgenologic signs of scurvy in 1 infant when the daily intake of ascorbic acid was 25 mg. points to the wisdom of the recommendation of the National Nutrition Conference of the National Research Council [8] that children under 1 year of age should receive at least 30 mg. of this vitamin daily. The development of frank clinical scurvy in another infant during an attack of pertussis also

3. Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, 1936, vol. 1, chap. 26, p. 12.

4. Pierce, H. B.: J. Nutrition **10**:689, 1935. Groen, J.: J. Clin. Investigation **16**:245, 1937.

5. Brock, J.: Biologische Daten für den Kinderarzt, Berlin, Julius Springer, 1932, vol. 1, chap. 5, p. 213. Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, 1936, vol. 1, chap. 25, p. 14.

6. Marriott, W. M., and Jeans, P. C.: Infant Nutrition, ed. 3, St. Louis, C. V. Mosby Company, 1941, p. 193. Gershon-Cohen, J.; Shay, H., and Fels, S. S.: Am. J. Roentgenol **46**:876, 1941. Hargreaves, F.; Fletcher, A. A., and Dickson, W. H.: Tr. Roy. Soc. Canada (sect. 5, biol. sc.) **25**:197, 1931.

7. Sparks, M. J., and Collins, E. N.: Am. J. Digest. Dis. **2**:618, 1935.

8. Proceedings of the National Nutrition Conference for Defense, Federal Security Agency, Washington, D. C., May 26-28, 1941, p. xi.

serves to emphasize the need for an abundant daily intake of this important vitamin, especially in the presence of a continuing infection such as pertussis.

SUMMARY

Minor changes in composition without alterations in caloric value or in protein content of a standard modified milk mixture for infant feeding,[2] namely, (1) raising the lactose-fat ratio, (2) substituting 1.6 per cent corn syrup for an equal quantity of lactose in the presence of an increased carbohydrate-fat ratio and (3) raising the lactose-fat ratio but omitting the addition of thiamine, were reflected by changes in the frequency of stools, especially in the first few months of life. Each change resulted in an increase in the average number of daily stools. The greatest increase in stool frequency accompanied the use of modified milk mixture 1, with raised lactose-fat ratio the only change.

These findings are interpretated as indicating (*a*) that a moderate increase in the lactose content exerts a positive laxative effect and (*b*) that modified milk mixtures (such as mixture 3) containing but 35 to 55 U. S. P. units of vitamin B_1 (thiamine) per quart (0.95 liter) produce a lessened stool frequency suggestive of a possible subclinical B_1 hypovitaminosis.

Mrs. Elizabeth Brown supervised the home feeding of the infants.

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BASAL METABOLISM OF NORMAL BOYS AND GIRLS FROM TWO TO TWELVE YEARS OLD, INCLUSIVE

REPORT OF A FURTHER STUDY

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As a report of progress of the basal metabolism project of the Child Research Council, Lewis, Kinsman and Iliff [1] published in 1937 the results of 637 determinations of basal metabolism on 93 normal children from 2 to 12 years old, inclusive. It was suggested at that time that final conclusions concerning standards for the basal metabolism of children of these ages could be drawn only when additional data were obtained and were shown not to differ significantly from the values then being reported. Since that time further study of children in this same age range has resulted in 946 new determinations on 102 children. It is the purpose of this paper to report the mean values for these new data and to compare them with the values previously published from this laboratory.[1]

EXPERIMENTAL PROCEDURE AND SUBJECTS

The experimental procedure has been essentially that previously reported in detail by Lewis, Kinsman and Iliff,[1] and only a brief description will be given here. The open circuit chamber method of Higgins and Bates [2] has been used in conjunction with gas analysis by the Carpenter [3] modification of the Haldane apparatus. The accuracy of the two apparatus used for gas analysis has been checked about once a week by analysis of outdoor air. The results of 415 analyses obtained between April 1, 1936 and Jan. 15, 1941 show that the values for carbon dioxide varied between 0.027 and 0.033 volumes per cent, with a mean value of 0.030, while the determinations of oxygen varied between 20.935 and 20.948 volumes per cent, with a mean value of 20.942. These average values, which check exactly those obtained in the earlier work, have been used in calculating all respiratory quotients.

Quantitative alcohol checks of the procedure have been made at three month intervals as outlined by Lewis, Kinsman and Iliff.[1] Most of these have been made alternately on the two chambers used for this study, but occasionally a smaller chamber designed for the determination of the basal metabolism of infants has been used. On eighteen such alcohol checks, 44 determinations of carbon dioxide production and oxygen consumption gave results which fall within ±2.0 per cent of the theoretic values for the combustion of ethyl alcohol and show a mean percentage deviation of −0.4 per cent. The mean of the observed values

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From the Child Research Council and the Department of Biochemistry of the University of Colorado School of Medicine.

This report is taken from the dissertation submitted by Anna Marie Duval to the faculty of the graduate school of the University of Colorado, June 1942, in partial fulfilment of the requirements for the degree Doctor of Philosophy.

1. Lewis, R. C.; Kinsman, G. M., and Iliff, A.: The Basal Metabolism of Normal Boys and Girls from Two to Twelve Years Old, Inclusive, Am. J. Dis. Child. **53**:348 (Jan.) 1937.

2. Higgins, H. L., and Bates, V.: New Method for the Determination of the Basal Metabolism of Babies and Small Children, Am. J. Dis. Child. **39**:71 (Jan.) 1930.

3. Carpenter, T. M.: An Apparatus for the Exact Analysis of Air in Metabolism Investigations with Respiratory Exchange Chambers, J. Metab. Research **4**:1, 1923. Carpenter, T. M.; Fox, E. L., and Sereque, A. F.: The Carpenter Form of the Haldane Gas Analysis Apparatus, J. Biol. Chem. **83**:211 (July) 1929.

for the respiratory quotient checks exactly the theoretic value of 0.667 for ethyl alcohol. The detailed results of these alcohol checks are on record elsewhere.[4]

The subjects of the determinations of basal metabolism have been members of the group of healthy children who are being studied regularly by the Child Research Council from birth to maturity. They are from private homes in Denver and vicinity, and their families represent all classes of society except the lowest stratum from an economic standpoint. All of the subjects under observation have been examined periodically by the members of the pediatric staff of the Council, and none has been found to fall outside the range of variation for healthy children. Anthropometric measurements have placed all subjects in the zone of normal body build.

All determinations of basal metabolism have been made in the morning, when the child had not eaten since the evening meal of the previous day. A preliminary rest period of at least twenty minutes and in most cases thirty minutes has preceded the determinations. Rest periods of this length have been found satisfactory for reaching basal levels of metabolism, provided the children are brought to the laboratory by automobile soon after arising and are spared any undue activity. This procedure has been followed rigidly in this study. Repeated observations have been made on each child, usually at intervals of from three to five months.

EXPERIMENTAL RESULTS

In the present study 551 determinations on 56 boys and 395 determinations on 46 girls, all of whom were between the ages of 2 and 12 years, inclusive, have been obtained. These represent all satisfactory determinations made on children of these ages between April 1, 1936 and Jan. 15, 1941. Space will not permit publication of the detailed data, but these are on record elsewhere.[4] Many of the children studied by Lewis, Kinsman and Iliff [1] have furnished data in an older age grouping in the present study. New children fall for the most part in the younger age ranges. As in the previous publication, ages have been computed as years and full months. Although repeated determinations have been made on each child, the data have been treated in a cross sectional manner, so that in most cases each child has been considered a new subject with each determination. The only exception to this general rule has been that when determinations have been repeated at intervals of less than three months these results have been averaged and the mean value has been used as a single determination.

In order to permit comparison of the new data with those reported earlier,[1] the values have been grouped in a manner similar to that used in the first report. Thus, the two sexes have been treated separately, and the values have been grouped according to age, weight, height and surface area with the class intervals for the last three factors so chosen that there are approximately the same number of groups for them as there are for age. The means and the coefficients of variation for each group have then been calculated for calories per hour, calories per hour per square meter, calories per hour per kilogram and calories per hour per centimeter, respectively, referred to age and for calories per hour referred to surface area, weight and height, respectively. The results of this statistical analysis have been made available [4] but will not be presented here, since they are in complete accord with those reported on the earlier data by Lewis, Kinsman and Iliff. The basal metabolism exhibits the lowest degree of scatter about the mean when expressed as calories per hour referred to weight and surface area, respectively, and as calories per hour per square meter referred to age. An intermediate

4. Duval, A. M.: A Study of the Basal Metabolism of Normal Children from Two to Fifteen Years Old, Inclusive, A dissertation on permanent deposit in the Charles Denison, M.D., Memorial Library, University of Colorado School of Medicine, Denver. Microfilm copy of the data on alcohol checks (table 1, part 1, pp. 20 and 21), on the individual basal metabolism determinations (tables 2 and 3, part 1, pp. 25-74, incl.) and on the statistical analysis of these data (tables 5-9, incl., part 1, pp. 76-82, incl.) may be obtained from the librarian, University of Colorado, Boulder, Colo.

degree of scatter is found for calories per hour referred to height and for calories per hour per centimeter referred to age, while the greatest dispersion is shown by calories per hour and calories per hour per kilogram, respectively, referred to age.

In the report of Lewis, Kinsman and Iliff [1] tentative standards were established on the basis of the mean values for calories per hour per square meter in relation to age and calories per hour in relation to weight, height and surface area, respectively. Accordingly, the comparison of the results of the present and of the earlier study will be confined to the mean values for basal metabolism obtained

TABLE 1.—*Significance of the Differences Between the Means Reported Earlier [1] for Calories per Hour per Square Meter Referred to Age and Those of the Present Study*

	Boys—Calories per Hour per Square Meter			Girls—Calories per Hour per Square Meter		
Age, Years	Mean (m_1), Former Study	Mean (m_2), Present Study	$\frac{m_1 - m_2}{\sigma_D}$	Mean (m_1), Former Study	Mean (m_2), Present Study	$\frac{m_1 - m_2}{\sigma_D}$
2 - 3	54.0	57.2	−3.5*	51.7	53.1	−2.0
3 - 4	52.7	54.0	−2.0	50.6	50.2	+0.7
4 - 5	51.2	52.0	−1.4	49.4	49.2	+0.2
5 - 6	50.4	50.5	±0.0	48.1	47.8	+0.5
6 - 7	48.7	49.0	−0.6	46.6	46.1	+0.9
7 - 8	48.2	46.5	+2.6	45.2	44.4	+1.3
8 - 9	46.3	45.1	+1.9	44.0	43.2	+1.1
9 -10	45.4	43.8	+2.3	42.1	42.5	−0.5
10 -11	44.5	41.9	+3.8*	40.8	40.4	+0.7
11 -12	41.7	41.5	+0.2	....	39.8	.....
12 -13	41.7	41.6	±0.0	....	39.6	.....

* This value is greater than 3 and thus denotes a significant difference for this class interval.

TABLE 2.—*Significance of the Differences Between the Means Reported Earlier [1] for Calories per Hour Referred to Weight and Those of the Present Study*

	Boys—Calories per Hour				Girls—Calories per Hour		
Weight, Kg.	Mean (m_1), Former Study	Mean (m_2), Present Study	$\frac{m_1 - m_2}{\sigma_D}$	Weight, Kg.	Mean (m_1), Former Study	Mean (m_2), Present Study	$\frac{m_1 - m_2}{\sigma_D}$
12-13	30.9	32.4	−2.6	12-13	29.8	30.1	−0.6
14-15	33.6	34.6	−2.0	14-15	32.2	32.6	−1.0
16-17	36.5	36.7	−0.7	16-17	35.1	35.1	±0.0
18-19	38.7	39.2	−1.2	18-19	36.8	37.2	−0.9
20-21	41.1	41.1	±0.0	20-21	39.2	38.4	+1.4
22-23	43.5	42.6	+1.7	22-23	41.1	40.3	+1.3
24-25	45.9	44.1	+2.8	24-25	42.5	41.2	+1.6
26-27	45.8	45.1	+1.1	26-27	44.7	42.2	+3.5*
28-29	47.5	46.8	+1.1	28-29	47.0	45.6	+1.3
30-31	48.8	47.6	+1.0	30-31	....	46.2	.....
32-33	50.0	49.1	+0.7	32-33	....	47.7	.....
34-35	51.4	50.4	+0.9	34-35	47.6	49.0	−1.4

* This value is greater than 3 and thus denotes a significant difference for this class interval.

by these four methods of reference. In order to test the significance of the differences between these mean values, the standard errors of the differences between the means for similar class intervals have been calculated by the following formula: $\sigma_D = \sqrt{\sigma_{m_1}^2 + \sigma_{m_2}^2}$ in which σ_{m_1} represents in each case the standard error of the mean of the old data and σ_{m_2} the standard error of the mean of the new data. The ratio of the difference between the means to the standard error of the difference has then been computed, and the criterion used to select those differences which are significant has been taken as a value of 3 or greater for this ratio. These ratios, together with the means of the two studies, are presented in table 1 for

calories per hour per square meter referred to age and in tables 2, 3 and 4 for calories per hour referred to weight, height and surface area, respectively. It may be seen that the new mean value for calories per hour per square meter in boys is significantly higher than the old value at the 2 year age level and significantly lower in the 10 year age group. No other significant differences are shown in the data on boys. Two instances of significant deviation occur for the girls, one in the grouping of 26 to 27 Kg., inclusive, when calories per hour are referred to weight and the other in the grouping of 0.97 to 1.03 square meters, inclusive, when calories per hour are referred to surface area. Otherwise, significant differences do not occur between the mean values obtained for the first series of data reported and those of the present study.

TABLE 3.—*Significance of the Differences Between the Means Reported Earlier* [1] *for Calories per Hour Referred to Height and Those of the Present Study*

Boys—Calories per Hour				Girls—Calories per Hour			
Height, Cm.	Mean (m_1), Former Study	Mean (m_2), Present Study	$\frac{m_1 - m_2}{\sigma_D}$	Height, Cm.	Mean (m_1), Former Study	Mean (m_2), Present Study	$\frac{m_1 - m_2}{\sigma_D}$
86- 92	31.1	32.2	−1.5	84- 90	28.3	28.6	−0.3
93- 99	33.1	34.1	−1.8	91- 97	30.5	30.6	−0.2
100-106	36.2	35.9	+0.6	98-104	32.8	33.1	−0.5
107-113	37.9	38.8	−2.1	105-111	36.0	35.9	+0.4
114-120	40.6	41.5	−1.9	112-118	37.8	37.1	+1.3
121-127	43.7	43.5	+0.3	119-125	41.2	39.9	+2.0
128-134	46.4	45.6	+1.7	126-132	43.9	42.0	+2.9
135-141	49.0	47.7	+1.7	133-139	46.6	45.4	+1.2
142-148	50.3	49.8	+0.5	140-146	47.9	49.0	−1.0

TABLE 4.—*Significance of the Differences Between the Means Reported Earlier* [1] *for Calories per Hour Referred to Surface Area and Those of the Present Study*

Boys—Calories per Hour				Girls—Calories per Hour			
Body Surface, Sq. M.	Mean (m_1), Former Study	Mean (m_2), Present Study	$\frac{m_1 - m_2}{\sigma_D}$	Body Surface, Sq. M.	Mean (m_1), Former Study	Mean (m_2), Present Study	$\frac{m_1 - m_2}{\sigma_D}$
0.52-0.58	31.0	32.4	−2.1	0.55-0.61	30.3	30.5	−0.5
0.59-0.65	33.3	34.2	−1.6	0.62-0.68	32.5	33.0	−1.1
0.66-0.72	36.1	36.5	−1.1	0.69-0.75	35.5	35.8	−0.5
0.73-0.79	38.4	39.0	−1.5	0.76-0.82	37.3	37.3	±0.0
0.80-0.86	41.2	41.5	−0.6	0.83-0.89	40.2	39.2	+1.9
0.87-0.93	43.7	43.0	+1.3	0.90-0.96	42.7	41.2	+2.2
0.94-1.00	46.1	45.0	+2.2	0.97-1.03	45.1	42.4	+3.7*
1.01-1.07	46.8	46.2	+0.9	1.04-1.10	47.0	46.5	+0.5
1.08-1.14	48.7	48.2	+0.7	1.11-1.17	47.2	48.0	−0.9
1.15-1.21	50.4	49.6	+0.7				
1.22-1.28	54.1	51.6	+2.5				

* This value is greater than 3 and thus denotes a significant difference for this class interval.

COMMENT

With the few exceptions noted, the data reported by Lewis, Kinsman and Iliff [1] in 1937 for the basal metabolism of children from 2 to 12 years old, inclusive, have been verified by the data collected more recently. The fact that only a few isolated groups have shown significant differences between the means of the two studies suggest sampling as their cause. If this is a valid assumption, a weighted average of the means of each of these groups would be more truly representative of the standard basal metabolism for the respective groups than either of the means found in the two studies. It will be found that none of the weighted means thus obtained for these isolated groups shows a significant difference from either of the individual means from which it is derived. Consequently, such weighted means may be

considered valid measures of the basal metabolism for these groups, and the reliability of the entire data presented in these two reports is thus established. Accordingly, in a later presentation [5] the combined data of both of these studies will be used to establish standards for the basal metabolism of children.

Lewis, Kinsman and Iliff [1] made a complete comparison of the data reported by them with the results of those studies which had appeared in the literature to 1936. Since the new mean values herein reported check those of the former study from this laboratory so closely, it would be superfluous to compare these new values with the results of the older reports in the literature. Accordingly, these new means will be compared only with the results of those studies on children from 2 to 12 years old, inclusive, which have appeared in the literature since 1936.

In three instances average values only have been reported and the comparison must of necessity be made on this basis. The percentage deviations with regard to sign of the mean values of Boothby, Berkson and Dunn,[6] of Shock and Soley [7] and of Shock [8] for calories per hour per square meter referred to age from those reported here are presented in table 5. It may be seen that the mean values of

TABLE 5.—*Percentage Deviations with Regard to Sign of the Mean Values Reported by Certain Other Investigators for Calories per Hour per Square Meter Referred to Age from Those of the Present Study*

	Mean Age	Percentage Deviation	
		Boys	Girls
Boothby, Berkson and Dunn [6]	6	+ 7.0	+ 7.9
	7	+ 9.8	+10.8
	8	+13.3	+ 4.8
	9	+14.9	+ 8.4
	10	+12.8	+10.9
	11	+14.4	+14.9
	12	+13.0	+10.8
Average		+12.2	+ 9.8
Shock and Soley [7]	12	+ 8.4	+ 8.3
Shock [8]	11.5	+ 5.1	+ 4.5
	12.5	+ 6.7	+ 2.0
Average		+ 5.9	+ 3.2

Boothby, Berkson and Dunn average 12.2 per cent higher for the boys and 9.8 per cent higher for the girls than the results on children from 6 to 12 years old, inclusive, in the present study. These authors have stressed the fact that their standards are based solely on the first satisfactory determination on any subject, even in cases in which several observations were made either on the same or on different days. This procedure was followed on the premise that the element of training should be excluded from normal standards. The results of the present study have been obtained from children on whom determinations were repeated at three to five month intervals and thus would be influenced by training, if it has any effect on basal metabolism. However, a comparison of the results of the first and

5. Lewis, R. C.; Duval, A. M., and Iliff, A.: Standards for the Basal Metabolism of Children from Two to Fifteen Years Old, Inclusive, J. Pediat., to be published.

6. Boothby, W. M.; Berkson, J., and Dunn, H. L.: Studies of the Energy of Metabolism of Normal Individuals: A Standard for Basal Metabolism with a Nomogram for Clinical Application, Am. J. Physiol. **116**:468 (July) 1936.

7. Shock, N. W., and Soley, M. H.: Average Values for Basal Respiratory Functions in Adolescents and Adults, J. Nutrition **18**:143 (Aug.) 1939.

8. Shock, N. W.: Standard Values for Basal Oxygen Consumption in Adolescents, Am. J. Dis. Child. **64**:19 (July) 1942.

second satisfactory determinations on the children of this group has revealed no consistent difference which could be attributed to training. This matter will be elaborated in a subsequent report from this laboratory.[9] It is evident, then, that the repetition of determinations on the same individuals, as was the practice in the present study, does not explain the finding of lower values than those reported by Boothby and co-workers. The average values reported by Shock and Soley in 1939 for 12 year old children are 8.4 per cent higher for the boys and 3.3 per cent higher for the girls than those of this study. The report of Shock on 11 and 12 year old children presents values which average 5.9 per cent higher for the boys and 3.2 per cent higher for the girls than those of this study.

For those studies in the literature in which individual data have been reported, histograms of the frequency distribution of the percentage deviations of these individual data from the mean values of the present study have been constructed. These histograms are presented as charts 1 to 5, inclusive. Whenever possible,

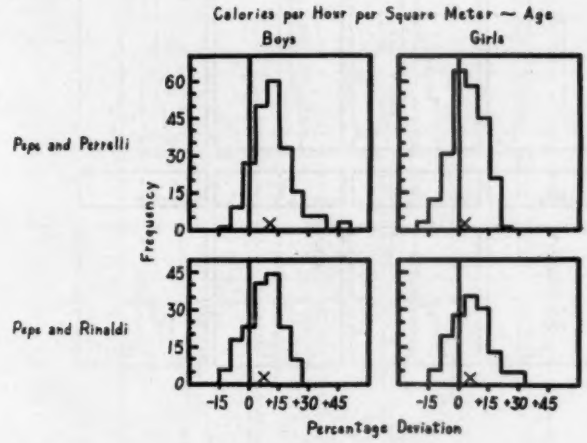

Chart 1.—Histograms of the percentage deviations of the individual results for both boys and girls reported by the investigators indicated on the chart from the mean values of the present study. × represents the mean percentage deviation with regard to sign.

comparison has been made on the basis of calories per hour per square meter in relation to age and calories per hour in relation to weight, height and surface area, respectively. In some instances the comparison could not be made in all four ways, either because the necessary values were not reported or because some of the children studied by the other workers did not fall within the range for weight, height or surface area of the children of this study.

It may be seen that particularly close agreement exists between the data for the girls of this study and those of Nakagawa,[10] Occhiuto and Cappelletto,[11] Pepe and

9. Lewis, R. C.; Duval, A. M., and Iliff, A.: The Effect of Training on the Basal Metabolism of Children, to be published.

10. Nakagawa, I.: Growth and Basal Metabolism: V. Basal Metabolism of High School Children, Am. J. Dis. Child. **53**:985 (April) 1937; VI. Changes in the Basal Metabolism of Children During Puberty, ibid. **53**:991 (April) 1937.

11. Occhiuto, A., and Cappelletto, A.: Contributo alla conoscenza del metabolismo di base degli Italiani: IX. Il metabolismo di base di soggetti (femmine) degli 11 ai 40 anni, Quad. Nutrizione **6**:290, 1939.

Perrelli,[12] Talbot,[13] Wang [14] and Wang, Kaucher and Wing.[15] By all methods of reference used, the mean percentage deviations of the results of these studies from those of the present report fall within ± 5 per cent. The data of Nakagawa on boys show slightly greater deviation from the mean values of the present report than those on girls, particularly for calories per hour per square meter referred to age. The results on boys in the study of Talbot are comparatively lower than those on girls and range, on the average, from 8 to 11 per cent below the mean values of the present report. No explanation is evident for the greater deviations found for boys than for girls in the studies of Pepe and Perrelli and of Wang. The mean values

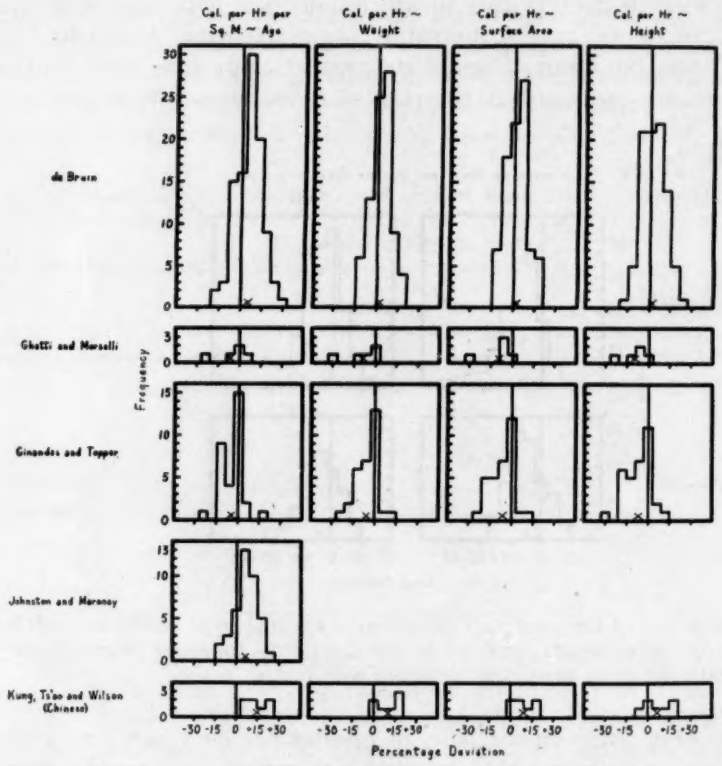
Cal. per Hr. per Sq. M. ~ Age
Cal. per Hr. ~ Weight
Cal. per Hr. ~ Surface Area
Cal. per Hr. ~ Height
de Bruin
Ghetti and Marselli
Ginsandes and Tepper
Johnston and Maroney
Kung, Ts'ao and Wilson (Chinese)
Frequency
-30 -15 0 +15 +30
Percentage Deviation

Chart 2.—Histograms of the percentage deviations of the individual results for boys reported by the investigators indicated on the chart from the mean values of the present study. × represents the mean percentage deviation with regard to sign.

of Wilson and Roy [16] for boys fall within the range of ± 5 per cent except when calories per hour are referred to height. With the exception of the values for

12. Pepe, M., and Perrelli, S.: Contributo alla conoscenza del metabolismo di base degli Italiani: III. Il metabolismo di base di soggetti dai 5 ai 17 anni, Quad. Nutrizione **4**:183, 1937.

13. Talbot, N. B.: Basal Energy Metabolism and Creatinine in the Urine: I. Observations on Children, Am. J. Dis. Child. **52**:16 (July) 1936.

14. Wang, C. C.: Basal Metabolism and Preformed and Total Creatinine in Urine of Seventy Children, Am. J. Dis. Child. **57**:838 (April) 1939.

15. Wang, C. C.; Kaucher, M., and Wing, M.: Metabolism of Adolescent Girls: I. Basal Metabolism and Energy Exchange, Am. J. Dis. Child. **51**:801 (April) 1936.

16. Wilson, H. E. C., and Roy, N. C.: Observations on the Basal Metabolism of Indian Boys in Calcutta, Indian J. M. Research **25**:901 (April) 1938.

calories per hour per square meter referred to age, the mean values of de Bruin [17] for both sexes also come well within this range. Many of the children observed by de Bruin were smaller than those of this study, and the more marked variations when age is taken into account might be explainable, at least in part, on this basis.

Somewhat above these values but deviating by less than + 10 per cent from the means of the present report are the average values of Johnston and Maroney,[18] Miana-Calabrese and Perrelli,[19] Pepe and Rinaldi,[20] Talbot, Wilson and Worcester [21] and Webster, Harrington and Wright.[22] The greater positive deviations of the results

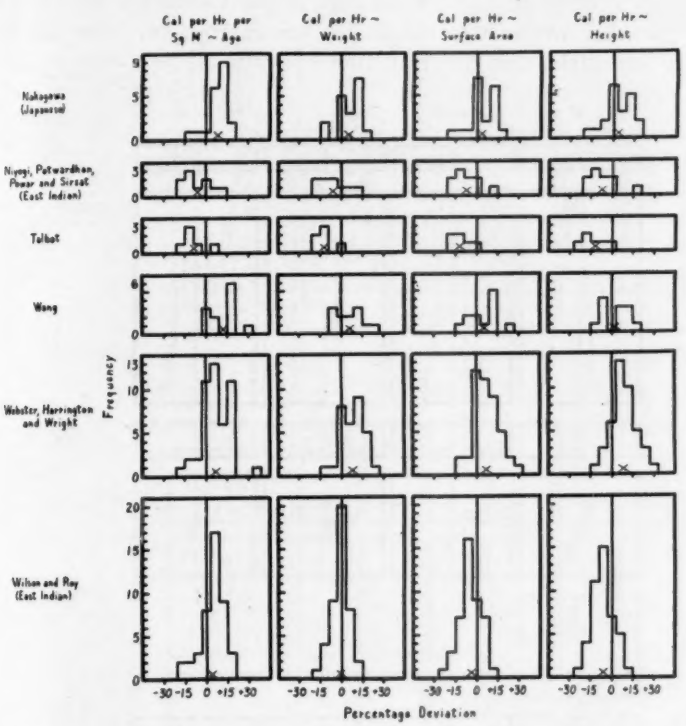
Cal per Hr per Sq M ~ Age
Cal per Hr ~ Weight
Cal per Hr ~ Surface Area
Cal per Hr ~ Height
Nakagawa (Japanese)
Niyogi, Patwardhan, Pawar and Sirsat (East Indian)
Talbot
Wang
Webster, Harrington and Wright
Wilson and Roy (East Indian)
Frequency
-30 -15 0 +15 +30
Percentage Deviation

Chart 3.—Histograms of the percentage deviations of the individual results for boys reported by the investigators indicated on the chart from the mean values of the present study. × represents the mean percentage deviation with regard to sign.

17. de Bruin, M.: Basal Metabolic Rate in Children with Abnormal Bodily Dimensions, Am. J. Dis. Child. **57**:29 (Jan.) 1939.

18. Johnston, J. A., and Maroney, J. W.: Relationship of Basal Metabolism to Dietary Intake, Am. J. Dis. Child. **51**:1039 (May) 1936. Maroney, J. W., and Johnston, J. A.: Caloric and Protein Requirements and Basal Metabolism of Children from Four to Fourteen Years Old, ibid. **54**:29 (July) 1937. Johnston, J. A., and Maroney, J. W.: Focal Infection and Metabolism: The Effect of the Removal of Tonsils and Adenoids on the Nitrogen Balance and the Basal Metabolism, J. Pediat. **12**:563 (May) 1938.

19. Miana-Calabrese, D., and Perrelli, S.: Contributo alla conoscenza del metabolismo di base degli Italiani: V. Il metabolismo di base di soggetti (femmine) dai 12 ai 20 anni, Quad. Nutrizione **4**:393, 1937.

20. Pepe, M., and Rinaldi, E.: Contributo alla conoscenza del metabolismo di base degli Italiani: II. Il metabolismo di base di soggetti dai 5 ai 15 anni, Quad. Nutrizione **3**:443, 1936.

21. Talbot, F. B.; Wilson, E. B., and Worcester, J.: Basal Metabolism of Girls: Physiologic Background and Application of Standards, Am. J. Dis. Child. **53**:273 (Jan.) 1937.

22. Webster, B.; Harrington, H., and Wright, L. M.: The Standard Metabolism of Adolescence, J. Pediat. **19**:347 (Sept.) 1941.

of de Biehler [23] and of Kung, Ts'ao and Wilson [24] do not merit great consideration, since they have probably arisen because of the small number of determinations in these studies.

By all methods of reference used, the results of Ghetti and Morselli,[25] Ginandes and Topper [26] and Niyogi, Patwardhan, Powar and Sirsat [27] average from 4 to 10 per cent lower than the mean values from this laboratory.

When the individual data of all of these authors are considered, it is found that the great majority of the results fall within ± 15 per cent of the mean values of the present study by all four methods of reference used. When calories per hour per square meter are referred to age, 78 per cent of the values for boys and 87 per cent of those for girls are within this range. When calories per hour are referred to weight for boys and girls, this range includes 90 and 93 per cent, respectively,

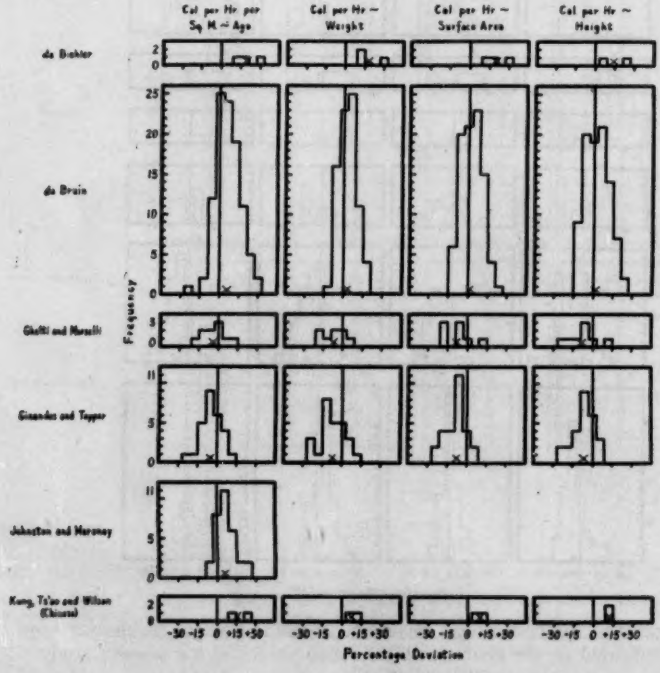

Chart 4.—Histograms of the percentage deviations of the individual results for girls reported by the investigators indicated on the chart from the mean values of the present study. × represents the mean percentage deviation with regard to sign.

of the results. When calories per hour are referred to surface area, 87 per cent of the results for boys and 91 per cent of those for girls are within ± 15 per cent of this

23. de Biehler, M.: Métabolisme basal et fonction métabolique de la glande thyroïde à l'époque de la puberté chez les filles, Arch. de méd. d. enf. **40**:274 (May) 1937.

24. Kung, L.; Ts'ao, C., and Wilson, S. D.: The Basal Metabolism of Chinese Children, Ten to Seventeen Years of Age, Chinese J. Physiol. **14**:431 (Dec.) 1939.

25. Ghetti, E., and Morselli, M.: Difficoltá ed accorgimenti nella determinazione del metabolismo basale della prima infanzia, Clin. pediat. **21**:433, 1939.

26. Ginandes, G. J., and Topper, A.: Insensible Perspiration in Children: III. Statistical Correlation of Insensible Perspiration and Basal Metabolism, Am. J. Dis. Child. **53**:705 (March) 1937; IV. The Influence of Salt, ibid. **55**:1176 (June) 1938.

27. Niyogi, S. P.; Patwardhan, V. N.; Powar, P. L., and Sirsat, M. V.: Studies on Basal Metabolism in Bombay: II. Basal Metabolism of Boys, Indian J. M. Research **28**:345 (Oct.) 1940.

mean, and when calories per hour are referred to height, 85 per cent of the results for boys and 91 per cent of those for girls fall within this range. Thus, when compared with the mean values reported in this study, the majority of determinations in the literature since 1936 fall within the accepted range for interindividual variation.

It is of interest to compare the various methods of reference for basal metabolism by considering the mean percentage deviations of all determinations in the literature cited from the mean values of this study. When calories per hour per square

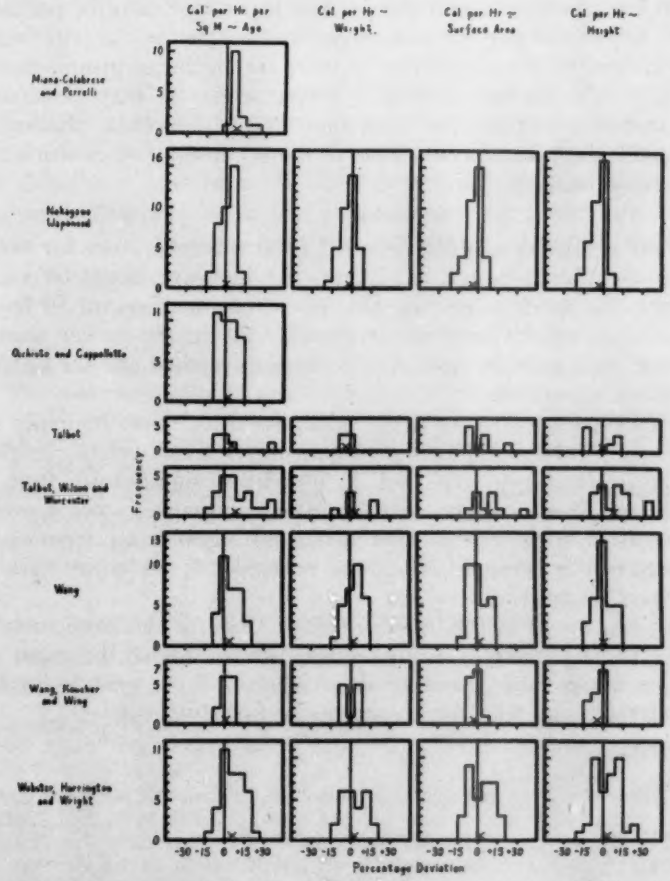

Chart 5.—Histograms of the percentage deviations of the individual results for girls reported by the investigators indicated on the chart from the mean values of the present study. × represents the mean percentage deviation with regard to sign.

meter are referred to age, the mean percentage deviations are + 7.3 per cent for the boys and + 4.5 per cent for the girls. This tendency for the results of the present study to average somewhat lower than those of other workers is less evident by the other methods of reference. When calories per hour are referred to weight, the mean percentage deviations are + 1.1 per cent for the boys and + 0.7 per cent for the girls. When calories per hour are referred to surface area, the comparable values are + 0.5 and + 0.3 per cent, respectively. When calories per hour are referred to height, the boys show a mean percentage deviation of + 0.3 per cent, while the girls show a value of + 0.7 per cent. Casual observation of these values

would lead to the implication that the greater deviation found when age is taken into account, as it is in referring calories per hour per square meter to age, is dependent on a greater variation in physiologic function in children of the same age as compared with children of the same size regardless of age. However, it must be remembered that the selection of data for comparison was made of necessity in such a way that all results for children within the age range from 2 to 12 years old, inclusive, have been compared with the mean values of the present report for calories per hour per square meter in relation to age, whereas only the results for children who fell within the ranges of body size of the children of this study could be compared with the mean values of the present report for calories per hour in relation to weight, height and surface area, respectively. Hence, the latter methods of reference were favored by the comparison of more homogeneous groups than were used in the case of the former method. Nevertheless, it may be concluded that the results of this report for the basal metabolism of normal children from 2 to 12 years old, inclusive, are representative of those found by other workers who have used comparable technics.

SUMMARY

In order that the results previously reported from this laboratory for the basal metabolism of normal children from 2 to 12 years old, inclusive, might be compared with additional data, the mean values for 551 new determinations on 56 boys and 395 new determinations on 45 girls are presented. As in the earlier study, the determinations were made with the open circuit chamber method and the Carpenter-Haldane gas analysis apparatus.

Except in four isolated groups, the mean values for calories per hour per square meter referred to age and for calories per hour referred to weight, height and surface area, respectively, herein reported do not differ significantly from those previously published. The exceptions are of little importance, since a weighted average of the means of these groups does not differ significantly from either of the means from which it is derived. Thus, the reliability of the entire data of the two studies has been established.

The individual data found in the literature since 1936 for the basal metabolism of children from 2 to 12 years old, inclusive, are compared with the mean values of this study. The latter values average from 0.3 to 7.3 per cent lower by the various methods of reference than the results in the literature cited.

4200 East Ninth Avenue.

BASAL METABOLISM OF NORMAL CHILDREN FROM THIRTEEN TO FIFTEEN YEARS OLD, INCLUSIVE

ROBERT C. LEWIS, PH.D.

ANNA MARIE DUVAL, PH.D.
AND
ALBERTA ILIFF, PH.D.
DENVER

The basal metabolism of normal children from 2 to 12 years old, inclusive, has been the subject of two reports from this laboratory, one by Lewis, Kinsman and Iliff [1] in 1937 and the other by Lewis, Duval and Iliff [2] more recently. Sufficient data have now been obtained to extend this age range through the sixteenth year. The purpose of this paper is to present, as a report of progress, the mean values of these basal metabolism determinations on normal children from 13 to 15 years old, inclusive.

EXPERIMENTAL PROCEDURE

The experimental procedure has been the same as that described by Lewis, Kinsman and Iliff.[1] The open circuit chamber method of Higgins and Bates,[3] in which gas analysis is carried out by the Carpenter [4] modification of the Haldane apparatus, has been used. The subjects of the basal metabolism determinations have been members of the group of healthy children who are being studied regularly by the Child Research Council from birth to maturity. Repeated determinations of basal metabolism have been made on each child, usually at intervals of from three to five months. In the observations on postpubertal girls no attempt has been made to avoid routine testing during any phase of the menstrual cycle. However, no determinations during which the subject experienced any pain have been considered satisfactory.

EXPERIMENTAL RESULTS

In this study 90 and 52 determinations of basal metabolism on 17 boys and 13 girls, respectively, all of whom were from 13 to 15 years old, inclusive, have been made. The results of these determinations, a detailed report of which may be obtained elsewhere,[5] have been grouped for the two sexes separately according

From the Child Research Council and the Department of Biochemistry of the University of Colorado School of Medicine.

This report is taken from the dissertation submitted by Anna Marie Duval to the faculty of the graduate school of the University of Colorado, June 1942, in partial fulfilment of the requirements for the degree Doctor of Philosophy.

1. Lewis, R. C.; Kinsman, G. M., and Iliff, A.: The Basal Metabolism of Normal Boys and Girls from Two to Twelve Years Old, Inclusive, Am. J. Dis. Child. **53**:348 (Jan.) 1937.

2. Lewis, R. C.; Duval, A. M., and Iliff, A.: The Basal Metabolism of Normal Boys and Girls from Two to Twelve Years Old, Inclusive: Report of a Further Study, Am. J. Dis. Child., this issue, p. 834.

3. Higgins, H. L., and Bates, V.: New Method for the Determination of the Basal Metabolism of Babies and of Small Children, Am. J. Dis. Child. **39**:71 (Jan.) 1930.

4. Carpenter, T. M.: An Apparatus for the Exact Analysis of Air in Metabolism Investigations with Respiratory Exchange Chambers, J. Metab. Research **4**:1, 1923. Carpenter, T. M.; Fox, E. L., and Sereque, A. F.: The Carpenter Form of the Haldane Gas Analysis Apparatus, J. Biol. Chem. **83**:211 (July) 1929.

5. Duval, A. M.: A Study of the Basal Metabolism of Normal Children from Two to Fifteen Years Old, Inclusive, a dissertation on permanent deposit in the Charles Deni-

(Footnote continued on next page)

to age, weight, height and surface area with the class intervals for the last three factors so chosen that there are approximately the same number of groups for them as there are for age. The mean and the standard deviation from the mean with their respective standard errors, as well as the coefficient of variation, have been

TABLE 1.—*Results of Statistical Analysis of 90 Basal Metabolism Determinations on 17 Boys from 13 to 15 Years Old, Inclusive (Analysis of Calories per Hour, Calories per Hour per Square Meter, Calories per Hour per Kilogram and Calories per Hour per Centimeter, Respectively, Referred to Age)*

	Age, Years	Mean ± Standard Error Thereof	Standard Deviation ± Standard Error Thereof	Coefficient of Variation, %
Calories per hour	13-14	57.6 ± 1.12	6.71 ± 0.79	11.7
	14-15	61.6 ± 1.16	6.65 ± 0.82	10.8
	15-16	64.0 ± 1.31	5.54 ± 0.92	8.6
			Mean	10.4
Calories per hour per square meter	13-14	41.4 ± 0.41	2.46 ± 0.29	5.9
	14-15	41.0 ± 0.42	2.44 ± 0.30	6.0
	15-16	39.9 ± 0.74	3.16 ± 0.53	7.9
			Mean	6.6
Calories per hour per kilogram	13-14	1.33 ± 0.022	0.133 ± 0.016	10.0
	14-15	1.28 ± 0.020	0.116 ± 0.014	9.0
	15-16	1.22 ± 0.026	0.111 ± 0.018	9.2
			Mean	9.4
Calories per hour per centimeter	13-14	0.367 ± 0.0051	0.0306 ± 0.0036	8.3
	14-15	0.375 ± 0.0052	0.0302 ± 0.0037	8.0
	15-16	0.376 ± 0.0074	0.0314 ± 0.0052	8.4
			Mean	8.2

TABLE 2.—*Results of Statistical Analysis of 52 Basal Metabolism Determinations on 13 Girls from 13 to 15 Years Old, Inclusive (Analysis of Calories per Hour, Calories per Hour per Square Meter, Calories per Hour per Kilogram and Calories per Hour per Centimeter, Respectively, Referred to Age)*

	Age, Years	Mean ± Standard Error Thereof	Standard Deviation ± Standard Error Thereof	Coefficient of Variation, %
Calories per hour	13-14	56.5 ± 1.05	5.04 ± 0.74	8.9
	14-15	56.8 ± 1.10	3.98 ± 0.78	7.0
	15-16	56.2 ± 1.13	4.07 ± 0.80	7.2
			Mean	7.7
Calories per hour per square meter	13-14	37.8 ± 0.52	2.48 ± 0.36	6.6
	14-15	36.0 ± 0.62	2.23 ± 0.44	6.2
	15-16	34.7 ± 0.46	1.66 ± 0.32	4.8
			Mean	5.9
Calories per hour per kilogram	13-14	1.16 ± 0.031	0.148 ± 0.022	12.7
	14-15	1.06 ± 0.038	0.136 ± 0.027	12.9
	15-16	1.02 ± 0.028	0.103 ± 0.020	10.0
			Mean	11.9
Calories per hour per centimeter	13-14	0.350 ± 0.0055	0.0262 ± 0.0039	7.5
	14-15	0.346 ± 0.0062	0.0224 ± 0.0044	6.5
	15-16	0.335 ± 0.0060	0.0218 ± 0.0043	6.5
			Mean	6.8

calculated for each group by the formulas used by Lewis, Kinsman and Iliff.[1] The results of this statistical analysis are reported in tables 1 to 4, inclusive.

On account of the impracticability of maintaining a rigid schedule for the repetition of basal metabolism determinations on the children of this study, the weighted

son, M.D., Memorial Library, University of Colorado School of Medicine, Denver. Microfilm copy of the data on the individual basal metabolism determinations (tables 1 and 2, part II, pp. 119-128, incl.) may be obtained from the Librarian, University of Colorado, Boulder, Colo.

means herein reported have been computed for varying numbers of determinations on different children. Thus, the possibility exists that in calculating these means undue weight may have been given to the results for the children who were studied more frequently. To determine whether this is true, the results for calories per hour per square meter referred to age have been recalculated in a manner that would give an even weight to each individual for each yearly period. The means for each child at each age period have been obtained and have been

TABLE 3.—*Results of Statistical Analysis of 90 Basal Metabolism Determinations on 17 Boys Between the Ages of 13 and 15 Years, Inclusive (Analysis of Calories per Hour Referred to Weight, Surface Area and Height, Respectively)*

		Calories per Hour		
	Range	Mean ± Standard Error Thereof	Standard Deviation ± Standard Error Thereof	Coefficient of Variation, %
Weight, Kg.	30-39	52.8 ± 0.73	3.18 ± 0.52	6.0
	40-49	59.4 ± 0.63	3.96 ± 0.44	6.7
	50-59	64.1 ± 1.00	4.24 ± 0.71	6.6
			Mean	6.4
Surface area, sq. m.	1.15-1.35	53.8 ± 0.74	3.69 ± 0.52	6.9
	1.36-1.56	59.9 ± 0.64	3.81 ± 0.45	6.4
	1.57-1.77	66.2 ± 1.21	5.54 ± 0.86	8.4
			Mean	7.2
Height, cm.	142-155	54.2 ± 0.80	3.92 ± 0.56	7.2
	156-169	60.9 ± 0.84	5.48 ± 0.60	9.0
	170-183	66.6 ± 1.36	6.22 ± 0.96	9.3
			Mean	8.5

TABLE 4.—*Results of Statistical Analysis of 52 Basal Metabolism Determinations on 13 Girls Between the Ages of 13 and 15 Years, Inclusive (Analysis of Calories per Hour Referred to Weight, Surface Area and Height, Respectively)*

		Calories per Hour		
	Range	Mean ± Standard Error Thereof	Standard Deviation ± Standard Error Thereof	Coefficient of Variation, %
Weight, Kg.	35-44	51.0 ± 1.32	3.96 ± 0.93	7.8
	45-54	57.2 ± 0.99	4.21 ± 0.70	7.4
	55-64	58.0 ± 0.60	2.76 ± 0.43	4.8
			Mean	6.7
Surface area, sq. m.	1.18-1.38	49.8 ± 1.58	3.88 ± 1.12	7.8
	1.39-1.59	57.5 ± 0.97	4.24 ± 0.69	7.4
	1.60-1.80	57.5 ± 0.64	3.11 ± 0.45	5.4
			Mean	6.9
Height, cm.	147-160	53.6 ± 1.25	4.83 ± 0.88	9.0
	161-174	57.8 ± 0.63	3.72 ± 0.44	6.4
			Mean	7.7

averaged to get the general mean for that year. When this is done, only an insignificantly small difference in the means is obtained from those reported in tables 1 and 2.

It may be seen from the mean values for the coefficient of variation in tables 1 to 4, inclusive, that the least scatter in the results on the boys occurs when calories per hour per square meter are referred to age and calories per hour are referred to weight and surface area, respectively. An intermediate degree of scatter is evidenced for calories per hour per centimeter referred to age and calories per hour referred to height, while the greatest variation is found for calories per hour per kilogram

and calories per hour, respectively, referred to age. These findings are essentially the same as those of Lewis, Kinsman and Iliff [1] and Lewis, Duval and Iliff [2] for children from 2 to 12 years old, inclusive. The results for the girls of the present study differ somewhat from those for the boys. The lowest degree of dispersion is shown not only for calories per hour per square meter referred to age and for calories per hour referred to weight and surface area, respectively, but also for calories per hour per centimeter referred to age. The value for calories per hour referred to age shows an intermediate rather than a large degree of scatter, while those for calories per hour referred to height and calories per hour per kilogram referred to age fall, as in the case of the boys, in the groups of intermediate and greatest dispersion, respectively. These discrepancies between the results for the girls and those for the boys may have arisen because of the comparatively small number of girls available for study in this age range.

COMMENT

A review of the literature reveals that there has been great interest in the basal metabolism of normal children from 13 to 15 years old, inclusive. As the results of the present study can be truly evaluated only in the light of the reports of other investigators, their data have been compared with the mean values herein reported. Whenever possible, such comparison has been made on the basis of calories per hour per square meter referred to age and calories per hour referred to weight, height and surface area, respectively. However, in some reports the necessary information for comparison in all of these ways has not been given; in other instances the comparison cannot be made on the basis of body size, because the children do not fall within the range for weight, height or surface area of the children of the present study.

In some of the earlier studies, individual data have not been reported. In such cases the comparison has been made solely on the basis of the mean percentage deviations with and without regard to sign from the mean values of the present report. Table 5 presents the results of such a comparison for twelve studies. The data of Benedict and Hendry,[6] of Benedict [7] and of Schlutz, Morse, Cassels and Iob [8] are reported in sufficient detail to permit comparison of the mean values by all four methods of reference. It may be seen that the mean percentage deviations with and without regard to sign do not exceed 5 per cent except when the results of Benedict and Hendry are compared on the basis of calories per hour referred to weight, and even in this instance the deviation amounts to only 6 per cent. The girls studied by Lewis [9] were, on the average, too short to be compared with those of this study, and this difference in size may explain the greater deviation when calories per hour are referred to weight and surface area, respectively, than when calories per hour per square meter are referred to age. It may be seen that

6. Benedict, F. G., and Hendry, M. F.: The Energy Requirements of Girls from Twelve to Seventeen Years of Age, Boston M. & S. J. **184**:217 (March 3); 257 (March 10); 282 (March 17); 297 (March 24); 329 (March 31) 1921.

7. Benedict, F. G.: The Basal Metabolism of Young Girls, Boston M. & S. J. **188**:127 (Feb. 1) 1923.

8. Schlutz, F. W.; Morse, M.; Cassels, D. E., and Iob, L. V.: A Study of the Nutritional and Physical Status and the Response to Exercise of Sixteen Negro Boys Thirteen to Seventeen Years of Age, J. Pediat. **17**:466 (Oct.) 1940.

9. Lewis, C. A.: Relation Between Basal Metabolism and Adolescent Growth, Am. J. Dis. Child. **51**:1014 (May) 1936.

the mean values of Molitch and Cousins,[10] of Shock and Soley [11] and of Shock,[12] when compared with those of the present study on the basis of calories per hour per square meter referred to age, check within 6 per cent with and without regard to sign. This is also true for the mean values of Bedale [13] for boys, but her results for girls are relatively higher. The results of Boothby, Berkson and Dunn [14] for children from 13 to 15 years old, inclusive, are as much above those of the present study as was the case when their younger children were compared with those of Lewis, Duval and Iliff.[2] It is not surprising that the results of Bailey [15] are high in view of the statement which accompanied these standards and described them as probably not "basal" but "normal" for the standard conditions of the test. The values of Lucas and Pryor [16] and of Molitch [17] for calories per hour referred to weight agree closely with those of the present study.

TABLE 5.—*Mean Percentage Deviations With and Without Regard to Sign of the Results of the Authors Cited from Those of the Present Study*

			Mean Percentage Deviation for							
			Calories per Hour per Square Meter Referred to Age		Calories per Hour Referred to Weight		Calories per Hour Referred to Surface Area		Calories per Hour Referred to Height	
Author	Sex	No. of Tests	Without Regard to Sign	With Regard to Sign	Without Regard to Sign	With Regard to Sign	Without Regard to Sign	With Regard to Sign	Without Regard to Sign	With Regard to Sign
Bailey [15]	M	..	12.6	+12.6	...	.....	...	.....	...	.....
	F	..	17.3	+17.3	...	.....	...	.....	...	.....
Bedale [13]	M	17	6.2	— 3.4	...	.....	...	.....	...	.....
	F	8	10.3	+ 6.9	...	.....	...	.....	...	.....
Benedict [7]	F	12	0	± 0	4.7	— 4.7	4.8	—4.8	1.3	+1.3
Benedict and Hendry [6]	F	72	4.8	— 1.9	6.2	— 6.0	5.1	—3.8	4.0	—2.2
Boothby, Berkson and Dunn [14]	M	74	13.0	+13.0	...	.....	...	.....	...	.....
	F	54	14.7	+14.7	...	.....	...	.....	...	.....
Lewis [9]	F	39	3.6	— 3.6	11.2	—11.2	9.1	—9.1	...	.....
Lucas and Pryor [16]	M	89	....	.....	3.0	— 1.5	...	.....	...	.....
	F	83	....	.....	2.2	— 2.1	...	.....	...	.....
Molitch [17]	M	88	....	.....	1.3	— 0.5	...	.....	...	.....
Molitch and Cousins [10]	M	104	6.3	— 4.3	...	.....	...	.....	...	.....
Schlutz, Morse, Cassels and Iob [6]	M	7	2.0	+ 2.0	2.2	+ 2.2	2.0	+2.0	2.2	+2.2
Shock [12]	M	300	4.2	+ 4.2	...	.....	...	.....	...	.....
	F	300	1.5	+ 0.9	...	.....	...	.....	...	.....
Shock and Soley [11]	M	50	6.1	+ 6.1	...	.....	...	.....	...	.....
	F	50	4.1	+ 4.1	...	.....	...	.....	...	.....

10. Molitch, M., and Cousins, R. F.: Variation of Basal Metabolic Rate per Unit Surface Area with Age, J. Nutrition **8**:247 (Aug.) 1934.

11. Shock, N. W., and Soley, M. H.: Average Values for Basal Respiratory Functions in Adolescents and Adults, J. Nutrition **18**:143 (Aug.) 1939.

12. Shock, N. W.: Standard Values for Basal Oxygen Consumption in Adolescents, Am. J. Dis. Child. **64**:19 (July) 1942.

13. Bedale, E. M.: Energy Expenditure and Food Requirements of Children at School, Proc. Roy. Soc., London, s.B **94**:368, 1923.

14. Boothby, W. M.; Berkson, J., and Dunn, H. L.: Studies of the Energy of Metabolism of Normal Individuals: A Standard for Basal Metabolism with a Nomogram for Clinical Application, Am. J. Physiol. **116**:468 (July) 1936.

15. Bailey, C. V., cited by Hawk, P. B., and Bergheim, O.: Practical Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1926, p. 896.

16. Lucas, W. P., and Pryor, H. B.: The Body Build Factor in the Basal Metabolism of Children, Am. J. Dis. Child. **46**:941 (Nov.) 1933.

17. Molitch, M.: Body Build Factor in the Basal Metabolism of Boys, Am. J. Dis. Child. **50**:621 (Sept.) 1935.

To facilitate the comparison of the results of this study with those of other reports in the literature in which the individual data for a minimum of 10 determinations on either boys or girls in this age range have been reported, histograms of the frequency distribution of the percentage deviations from the mean values of the present study have been constructed. These are presented as charts 1 to 4 inclusive, and a brief discussion of these histograms follows.

The mean percentage deviations of the results of Nakagawa,[18] of Topper and Mulier [19] and of Wilson and Roy [20] for boys and of the results of MacLeod,[21]

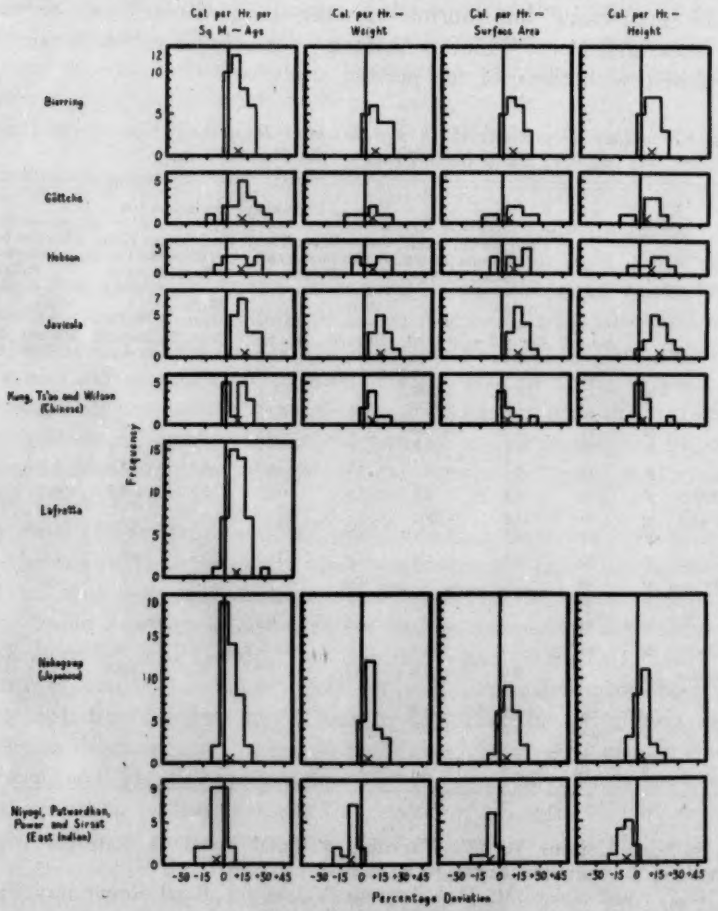

Chart 1.—Histograms of the percentage deviations of the individual results on boys reported by the investigators indicated on the chart from the mean values of the present study. × represents the mean percentage deviation with regard to sign.

18. Nakagawa, I.: Growth and Basal Metabolism: VI. Changes in the Basal Metabolism of Children During Puberty, Am. J. Dis. Child. **53**:991 (April) 1937.

19. Topper, A., and Mulier, H.: Basal Metabolism of Normal Children: The Puberty Reaction, Am. J. Dis. Child. **43**:327 (Feb.) 1932.

20. Wilson, H. E. C., and Roy, N. C.: Observations on the Basal Metabolism of Indian Boys in Calcutta, Indian J. M. Research **25**:901 (April) 1938.

21. MacLeod, G.: Studies of the Normal Basal Energy Requirement, New York, Columbia University Press, 1924.

of McKay [22] of Nylin,[23] of Wang, Kaucher and Wing [24] and of Webster, Harrington and Wright [25] for girls from the mean values of the present study are within ± 5 per cent. With the exception of a low value for calories per hour referred to weight, the mean percentage deviations of the results for the girls in the study of Nakagawa are also within ± 5 per cent. No explanation is at hand for the relatively high values found by Topper and Mulier for the girls of their study. The values of Webster, Harrington and Wright for boys show somewhat greater deviation from

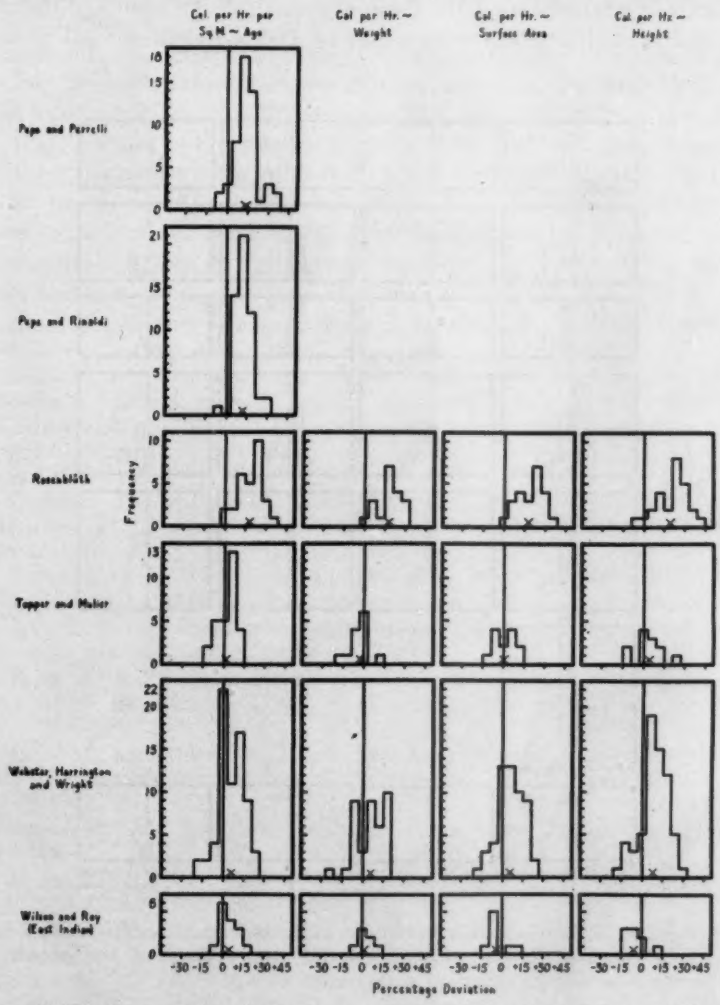
Cal. per Hr. per Sq. M. ~ Age
Cal. per Hr. ~ Weight
Cal. per Hr. ~ Surface Area
Cal. per Hr. ~ Height
Pepe and Perrelli
Pepe and Rinaldi
Rosenbloth
Topper and Mulier
Webster, Harrington and Wright
Wilson and Roy (East Indian)
Frequency
Percentage Deviation
-30 -15 0 +15 +30 +45

Chart 2.—Histograms of the percentage deviations of the individual results on boys reported by the investigators indicated on the chart from the mean values of the present study. × represents the mean percentage deviation with regard to sign.

22. McKay, H.: Basal Metabolism of Young Women, Bulletin 465, Ohio Agricultural Experimental Station, 1930.

23. Nylin, G.: The Physiology of the Circulation During Puberty, Acta med. Scandinav. (supp.) **69**:1, 1935.

24. Wang, C. C.; Kaucher, M., and Wing, M.: Metabolism of Adolescent Girls: I. Basal Metabolism and Energy Exchange, Am. J. Dis. Child. **51**:801 (April) 1936.

25. Webster, B.; Harrington, H., and Wright, L. M.: The Standard Metabolism of Adolescence, J. Pediat. **19**:347 (Sept.) 1941.

those of this report than do their results for girls. The mean percentage deviations of the results of Kung, Ts'ao and Wilson [26] are within ± 5 per cent except when calories per hour per square meter are referred to age for both sexes and when calories per hour are referred to weight for boys. The mean percentage deviations of the results of Wang [27] for girls and of Göttche [28] for both sexes from the mean values of the present study are also within ± 5 per cent except when calories per hour per square meter are referred to age.

By all methods of reference used, the mean deviations of the results of Bierring,[29] of Hobson [30] and of Lafratta [31] for boys and of Miana-Calabrese and Perrelli,[32]

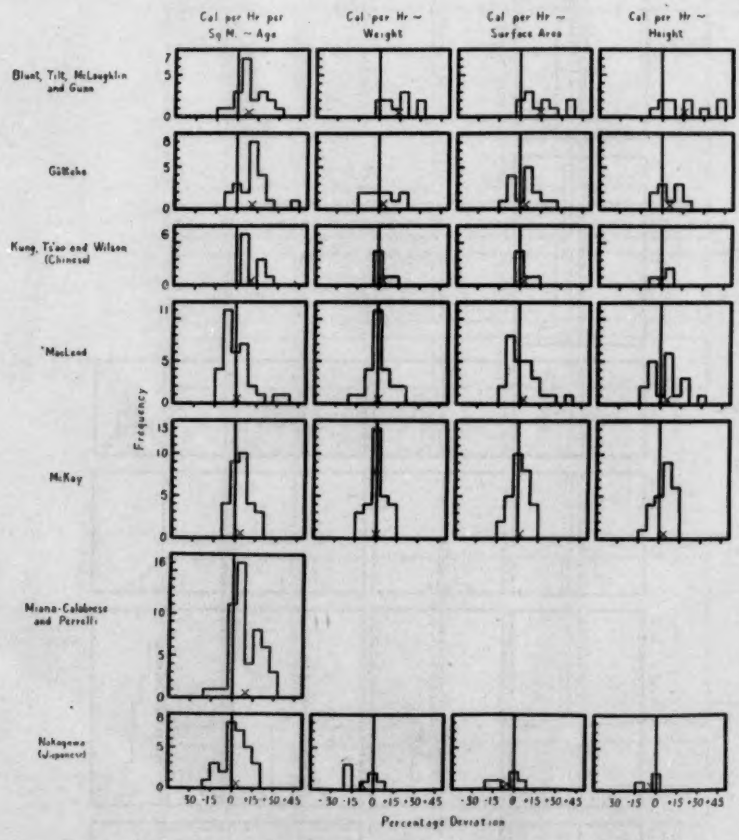

Chart 3.—Histograms of the percentage deviations of the individual results on girls reported by the investigators indicated on the chart from the mean values of the present study. × represents the mean percentage deviation with regard to sign.

26. Kung, L.; Ts'ao, C., and Wilson, S. D.: The Basal Metabolism of Chinese Children, Ten to Seventeen Years of Age, Chinese J. Physiol. **14**:431 (Dec.) 1939.

27. Wang, C. C.: Basal Metabolism of American-Born Chinese Girls and of American Girls of Same Age, Am. J. Dis. Child. **48**:1041 (Nov.) 1934; Basal Metabolism and Preformed and Total Creatinine in Urine of Seventy Children, ibid. **57**:838 (April) 1939.

28. Göttche, O.: Gasstoffwechseluntersuchungen im Kindesalter: Die Pubertätsreaktion, Monatschr. f. Kinderh. **32**:22, 1926.

29. Bierring, E.: The Standard Metabolism of Boys (Seven to Eighteen Years Inclusive), Copenhagen, Levin & Munksgaard, 1931.

30. Hobson, F. G.: A Comparative Study of Basal Metabolism in Normal Men, Quart. J. Med. **16**:363 (July) 1923.

of Occhiuto and Cappelletto [33] and of Talbot, Wilson and Worcester [34] for girls from those of the present study are not greater than + 10 per cent. The mean deviations of the results of Javicola [35] of Pepe and Perrelli,[36] of Pepe and Rinaldi [37] and of Rosenblüth [38] for boys and of Blunt, Tilt, McLaughlin and Gunn [39] for girls are greater than those noted in the data of the other authors cited.

Only in the study of Niyogi, Patwardhan, Powar and Sirsat [40] on East Indian boys are the mean percentage deviations from the results of the present study definitely on the negative side. Here the mean deviations are from — 5 to — 8 per cent, inclusive.

The number of determinations and the maximum, minimum and mean percentage deviations from the results of the present study for the individual data of those reports in which fewer than 10 determinations were obtained are presented in table 6. Obviously, because of the small number of cases involved, this comparison is of less significance than that made with the results of the studies just cited. It has been included merely for the sake of completeness. The mean percentage deviations of the results of Benedict and Talbot,[41] of Eaton [42] and of Johnston and Maroney [43] from the mean values of the present study are within ± 5 per cent. With the exception of the mean percentage deviation for calories per hour per square meter in relation to age, this is also true for the results of de Bruin [44] and of Olmstead,

31. Lafratta, E.: Contributo alla conoscenza del metabolismo di base degli Italiani: VI. Il metabolismo di base di soggetti (maschi) dai 14 ai 20 anni, Quad. Nutrizione **4**:410, 1937.

32. Miana-Calabrese, D., and Perrelli, S.: Contributo alla conoscenza del metabolismo di base degli Italiani: V. Il metabolismo di base di soggetti (femmine) dai 12 ai 20 anni, Quad. Nutrizione **4**:393, 1937.

33. Occhiuto, A., and Cappelletto, A.: Contributo alla conoscenza del metabolismo di base degli Italiani: IX. Il metabolismo di base di soggetti (femmine) degli 11 ai 40 anni, Quad. Nutrizione **6**:290, 1939.

34. Talbot, F. B.; Wilson, E. B., and Worcester, J.: Basal Metabolism of Girls: Physiologic Background and Application of Standards, Am. J. Dis. Child. **53**:273 (Jan.) 1937.

35. Javicola, I.: Il metabolismo basale ne pellagrosa e nel soggetto normale della popolazione rurale veneta, Quad. Nutrizione **4**:1, 1937.

36. Pepe, M., and Perrelli, S.: Contributo alla conoscenza del metabolismo di base degli Italiani: III. Il metabolismo di base di soggetti dai 5 ai 17 anni, Quad. Nutrizione **4**:183, 1937.

37. Pepe, M., and Rinaldi, E.: Contributo alla conoscenza del metabolismo di base degli Italiani: II. Il metabolismo di base di soggetti dai 5 ai 15 anni, Quad. Nutrizione **3**:443, 1936.

38. Rosenblüth, A.: Der Grundumsatz bei Kindern und Jugendlichen, Ztschr. f. Kinderh. **46**:531, 1928.

39. Blunt, K.; Tilt, J.; McLaughlin, L., and Gunn, K. B.: The Basal Metabolism of Girls, J. Biol. Chem. **67**:491 (Feb.) 1926.

40. Niyogi, S. P.; Patwardhan, V. N.; Powar, P. L., and Sirsat, M. V.: Studies on Basal Metabolism in Bombay: II. Basal Metabolism of Boys, Indian J. M. Research **28**: 345 (Oct.) 1940.

41. Benedict, F. G., and Talbot, F. B.: Metabolism and Growth from Birth to Puberty, Publication 302, Carnegie Institution of Washington, 1921.

42. Eaton, A. G.: The Basal Metabolic Rate of Normal Individuals in New Orleans, J. Lab. & Clin. Med. **24**:1255 (Sept.) 1939.

43. Johnston, J. A., and Maroney, J. W.: Focal Infection and Metabolism: The Effect of the Removal of Tonsils and Adenoids on the Nitrogen Balance and the Basal Metabolism, J. Pediat. **12**:563 (May) 1938. Maroney, J. W., and Johnston, J. A.: Caloric and Protein Requirements and Basal Metabolism of Children from Four to Fourteen Years Old, Am. J. Dis. Child. **54**:29 (July) 1937.

44. de Bruin, M.: Basal Metabolic Rate in Children of Abnormal Bodily Dimensions, Am. J. Dis. Child. **57**:29 (Jan.) 1939.

Barr and Du Bois.[45] The mean values of Benedict and Meyer [46] check those of the present study closely when calories per hour are referred to weight and surface area, respectively, but are much higher when calories per hour per square meter are referred to age and much lower for the only determination in which comparison could be made on the basis of calories per hour referred to height. In the one instance in which the data of N. B. Talbot [47] can be compared with those of the

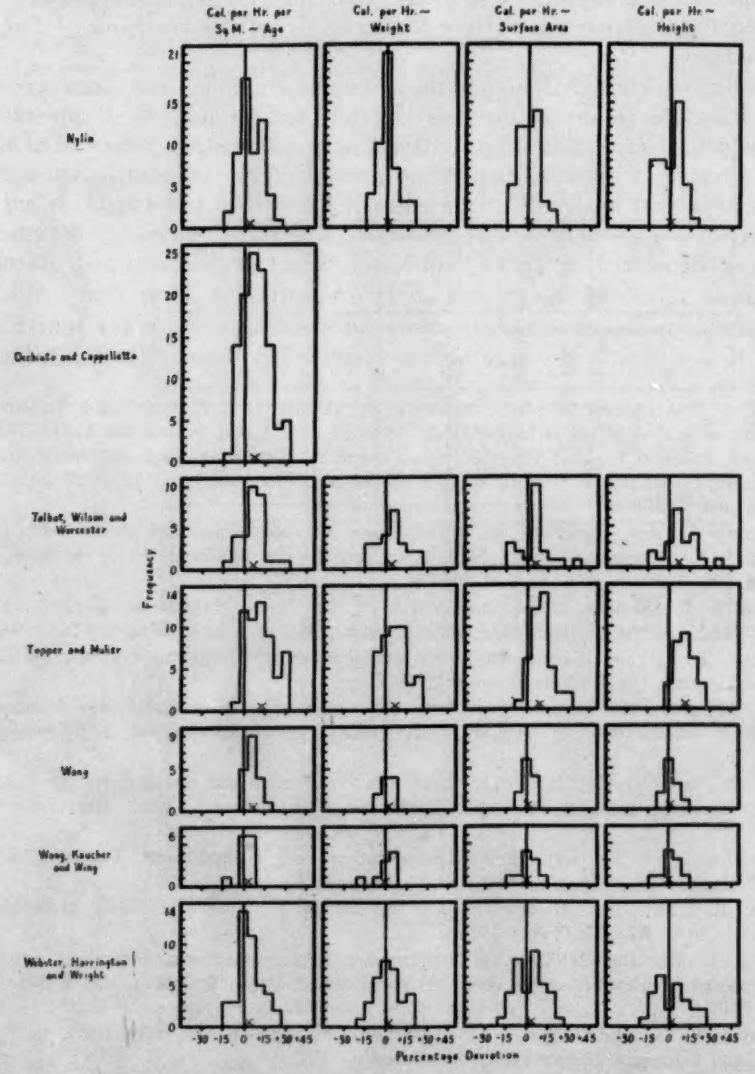

Chart 4.—Histograms of the percentage deviations of the individual results on girls reported by the investigators indicated on the chart from the mean values of the present study. × represents the mean percentage deviation with regard to sign.

45. Olmstead, W. H.; Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry: XXVII. Metabolism of Boys Twelve and Fourteen Years Old, Arch. Int. Med. **21**:621 (May) 1918.

46. Benedict, F. G., and Meyer, M. H.: The Basal Metabolism of American-Born Chinese Girls, Chinese J. Physiol. **7**:45 (March) 1933.

47. Talbot, N. B.: Basal Energy Metabolism and Creatinine in the Urine: I. Observations on Children, Am. J. Dis. Child. **52**:16 (July) 1936.

TABLE 6.—*Percentage Deviations of the Results of the Authors Cited from Those of the Present Study*

Authors	Sex	Calories per Hour per Square Meter Referred to Age				Calories per Hour Referred to Weight				Calories per Hour Referred to Surface Area				Calories per Hour Referred to Height			
		No. of Tests	Percentage Deviation			No. of Tests	Percentage Deviation			No. of Tests	Percentage Deviation			No. of Tests	Percentage Deviation		
			Maximum	Minimum	Mean		Maximum	Minimum	Mean		Maximum	Minimum	Mean		Maximum	Minimum	Mean
Benedict and Meyer [46] (Chinese)	F	6	+21.0	— 2.9	+15 3	3	+ 5.7	—11.8	— 2.6	3	+ 9.8	—11.8	— 0.4	1	.....	.....	—16.0
Benedict and Talbot [41]	M	3	+11.9	— 9.0	+ 1.0	3	+ 8.1	— 5.7	+ 0.7	3	+ 8.1	— 7.8	+ 1.1	3	+ 8.1	— 9.1	+ 1.2
	F	1	.....	.....	— 1.8												
de Bichler [48]	F	2	+20.0	+ 9.6	+14.8	2	+18.1	+10.5	+14.3	1	.....	.....	+10.9	1	.....	.....	+11.1
de Bruin [44]	M	7	+19.8	— 7.8	+ 6.2	4	+ 7.3	—10.6	— 0.5	4	+ 6.4	— 9.5	— 0.9	4	+ 8.5	—12.4	— 0.1
	F	5	+24.6	— 1.1	+13.7	3	+14.2	— 3.2	+ 2.7	3	+ 7.4	— 6.3	— 1.2	1	.....	.....	— 1.1
Du Bois [49]	M	4	+24.6	+15.0	+19 9												
Eaton [42]	M	1	.....	.....	+ 0.5												
	F	2	+ 0.2	— 4.8	— 2.3												
Ginandes and Topper [53]	M	1	.....	.....	— 6.0	1	.....	.....	— 6.0	1	.....	.....	— 7.8	1	.....	.....	— 9.4
Johnston and Maroney [43]	M	2	+ 7.7	+ 0.7	+ 4.2												
Magnus-Levy and Falk [50]	M	3	+15.6	+ 7.1	+10.7												
	F	2	+20.8	+19.7	+20.2												
Olmstead, Barr and Du Bois [45]	M	7	+24.2	— 3.2	+ 9.9	7	+17.4	— 7.8	+ 4.9	7	+18.0	— 5.4	+ 4.9	7	+18.2	— 2.6	+ 4.8
Orner [51]	M	8	+22.3	— 4.2	+ 8.9	6	+18.1	— 5.2	+ 7.1	6	+20.2	— 4.3	+ 8.3	7	+26.8	— 1.4	+12.5
F. B. Talbot [54]	M	2	— 7.5	—12.4	—10.0	2	— 7.0	—16.1	—11.0	2	— 7.0	—10.3	— 8.6	1	.....	.....	— 8.6
N. B. Talbot [47]	M	2	+ 4.2	+ 4.1	+ 4.2												
	F	1	.....	.....	+ 5.7	1	.....	.....	+ 1.5	1	.....	.....	— 7.6	1	.....	.....	— 9.0
Wang and Hawks [52] (Chinese)	F	2	+11.1	+ 9.7	+10.4												

present study on the basis of calories per hour in relation to surface area and height, respectively, his results are lower, but by the other methods of reference they check within ± 6 per cent. The mean values of de Biehler,[48] of Du Bois,[49] of Magnus-Levy and Falk,[50] of Orner [51] and of Wang and Hawks [52] are all higher than those of the present study, while the mean values obtained by Ginandes and Topper [53] and by F. B. Talbot [54] are lower.

Some interesting observations may be made if all individual data in the literature cited on children from 13 to 15 years old, inclusive, are combined. When calories per hour per square meter referred to age for these composite data are compared with the mean values of the present study, the mean percentage deviations are + 8.3 per cent for the boys and + 7.1 per cent for the girls. By the other methods of reference the deviations are not so marked. They are + 5.8 per cent for the boys and + 2.7 per cent for the girls when calories per hour are referred to weight, + 6.1 and + 3.8 per cent, respectively, for the boys and the girls when calories per hour are referred to surface area and + 7.2 and + 4.4 per cent, respectively, for the boys and the girls when calories per hour are referred to height. The smaller deviations seen when various measures of body size without regard to age are used as the methods of reference should not be given too great emphasis. It must be remembered that the mean percentage deviations for calories per hour per square meter in relation to age are based on all available data, whereas the deviations for calories per hour in relation to weight, height and surface area, respectively, are based of necessity only on determinations on those subjects within the range for body size of the children of this study. Thus, the smaller deviations by the latter methods of reference are probably due to the more homogeneous groups used for comparison. All of these values for the mean percentage deviations of the individual data in the literature from the mean values of the present study are greater than those reported by Lewis, Duval and Iliff [2] for younger children.

In evaluating the basal metabolism of 13, 14 and 15 year old children, consideration must be given to the possibility that the basal metabolism in this age range bears a relationship to the stage of adolescent development which has been attained. The effect of adolescence on the basal metabolism will be discussed in a subsequent report from this laboratory.[55]

SUMMARY

A study of the basal metabolism of children from 13 to 15 years old, inclusive, has yielded 90 determinations on 17 boys and 52 determinations on 13 girls. The means and the standard deviations from the means, together with their respective

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standard errors, and the coefficients of variation have been computed at convenient class intervals for calories per hour, calories per hour per square meter, calories per hour per centimeter and calories per hour per kilogram, respectively, in relation to age and for calories per hour in relation to weight, height and surface area, respectively.

A comparison of the mean coefficients of variation for each of these methods of expressing the basal metabolism reveals that the data on boys show the lowest degree of scatter about the mean for calories per hour per square meter referred to age and for calories per hour referred to weight and surface area, respectively. An intermediate degree of dispersion is evidenced for calories per hour per centimeter referred to age and for calories per hour referred to height, while the greatest variation is found for calories per hour per kilogram for calories per hour, respectively, referred to age. These findings are essentially the same as those previously reported from this laboratory [56] for children from 2 to 12 years old, inclusive.

The mean values for the coefficient of variation for the girls differ somewhat from those for the boys. The lowest degree of dispersion is shown not only for calories per hour per square meter referred to age and calories per hour referred to weight and surface area, respectively, but also for calories per hour per centimeter referred to age. The value for calories per hour referred to age shows an intermediate rather than a large degree of scatter, while calories per hour referred to height and calories per hour per kilogram referred to age fall, as in the case of the boys, in the groups of intermediate and greatest dispersion, respectively.

A detailed comparison has been made between the mean values obtained in this study for the basal metabolism of children 13, 14 and 15 years old and similar data reported in the literature.

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56. Lewis, Kinsman and Iliff.[1] Lewis, Duval and Iliff.[2]

SERUM CHOLESTEROL VALUES FOR INFANTS AND CHILDREN

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Because of the wide range of variation in the concentration of cholesterol in the blood serum of healthy adults,[1] confirmed in the present study for children, sufficiently large numbers of subjects to justify statistical comparison are required to establish relatively small deviations from normal. This condition has not been met in most previous studies of serum cholesterol in children. Furthermore, the methods used for determination of cholesterol have been criticized severely, and no measurements of cholesterol fractions have been reported in most of these investigations. During the period between Jan. 1, 1934 and March 1, 1942 the accurate method of Schoenheimer and Sperry [2] or a modification thereof was employed in the Babies Hospital in a large series of determinations of serum cholesterol on infants and children in the first thirteen years of life. It is the purpose of this report to evaluate these data. The clinical histories of all patients on whom determinations of serum cholesterol were made during this period were reviewed. Patients with diabetes, nephrosis or hypothyroidism, diseases in which unmistakably high serum cholesterol concentrations are frequently encountered, were excluded; and, since Bruch [3] has discussed the serum cholesterol values in obesity, patients with this complaint were likewise omitted. The variations in serum cholesterol during the first month of life have been reported by Sperry,[4] and infants in this age group were also excluded.

NORMAL SUBJECTS

Of the remaining patients 417 were regarded as normal. They showed no evidence of malnutrition, infection, severe anemia, hepatic disease or other metabolic disorders. They were first grouped according to age (table 1). Since there were

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no significant differences among the means of these groups, they were combined, to give a mean of 205.7 ± 38 (standard deviation) mg. of cholesterol per hundred cubic centimeters of serum for the period from the second month through the thirteenth year of life. The histogram of this group is included in chart 1.

The ratio of combined to free cholesterol was determined for 344 patients of this group. Table 2 gives a summary of these values arranged with respect to age. Again, because no clear trend was noted, the groups were combined, to give a mean ratio of 2.58 ± 0.29. The histogram of these data is included in chart 2.

TABLE 1.—*Total Cholesterol Content of Serum of Normal Subjects*

Age	Number	Mean in Mg./100 Cc.	Standard Deviation
2 to 6 months	16	200.2	±49
7 to 12 months	27	206.6	±35.6
2d year	40	203.2	±38
3d year	36	202.4	±30.5
4th year	29	194.0	±29
5th year	24	212.6	±38
6th year	28	208.6	±39
7th year	33	204.3	±32
8th year	25	204.3	±34
9th year	28	220.4	±42
10th year	36	205.8	±34
11th year	34	206.2	±42
12th year	33	210.4	±42
13th year	28	204.3	±32
Total	417		
Average	..	205.7	±38

TABLE 2.—*Ratio of Combined to Free Cholesterol in Serum of Normal Subjects*

Age	Number	Mean Ratio	Standard Deviation
2 to 6 months	14	2.32	±0.21
7 to 12 months	22	2.46	±0.29
2d year	31	2.43	±0.53
3d year	31	2.63	±0.28
4th year	20	2.57	±0.31
5th year	17	2.47	±0.05
6th year	25	2.58	±0.20
7th year	30	2.66	±0.20
8th year	22	2.64	±0.05
9th year	25	2.59	±0.04
10th year	24	2.73	±0.22
11th year	30	2.63	±0.28
12th year	29	2.63	±0.21
13th year	24	2.56	±0.25
Total	344		
Average	..	2.58	±0.29

Using the same method for determination of cholesterol, Sperry [1b] found a mean of 201 ± 44 mg. per hundred cubic centimeters of serum for 91 healthy subjects between the ages of 19 and 43 years. For the same series the ratio of combined to free cholesterol averaged 2.76 ± 0.18. It is a striking fact that both of these values are in close agreement with those found for normal children in the present study, and it may be concluded that by the second month of life the cholesterol concentration and the ratio of combined to free cholesterol have already increased from the low values found at birth to the adult level, where they remain without further change.

THE EFFECT OF LOSS OF WEIGHT AND MALNUTRITION

Patients who had a clearcut record of loss of weight but who were not suffering from anemia, from hepatic disease or, as far as could be discerned, from infection, were grouped together. Patients receiving thyroid extract were not included.

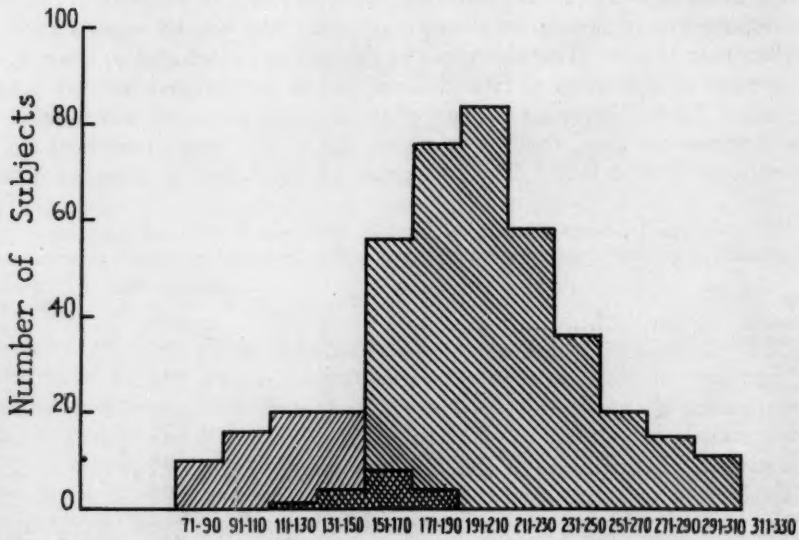

Chart 1.—Values for serum cholesterol (milligrams per hundred cubic centimeters). Lines extending downward from left to right indicate values for 417 normal subjects; lines extending upward from left to right indicate values for 78 subjects who were losing weight; cross hatching indicates overlapping values.

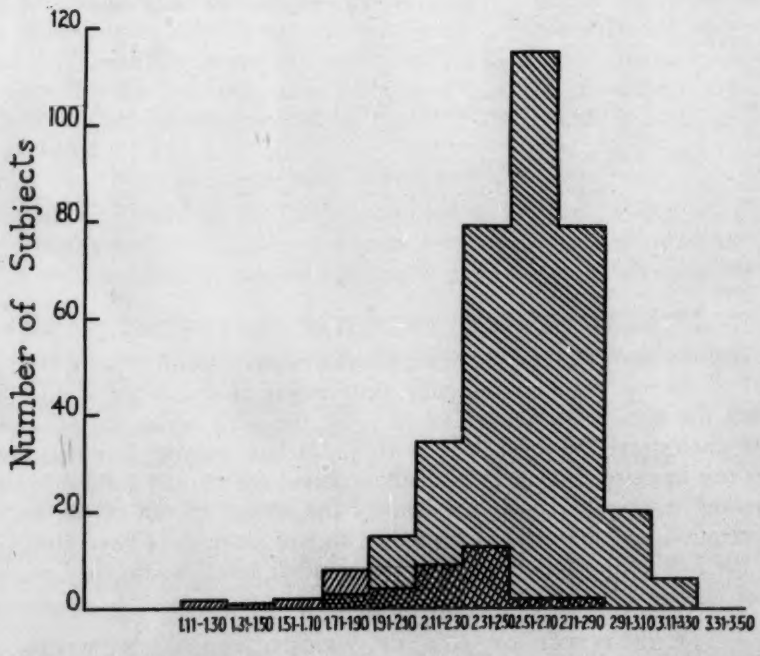

Chart 2.—Ratio of combined cholesterol to free cholesterol. Lines extending downward from left to right indicate values for 344 normal subjects; lines extending upward from left to right indicate values for 24 subjects who were losing weight; cross hatching indicates overlapping values.

There remained 78 patients, for most of whom a diagnosis of feeding problem or of the celiac syndrome had been made. The average concentration of total cholesterol in the serum was 123.0 ± 0.29 mg. per hundred cubic centimeters. The ratio of combined to free cholesterol was determined for 43 of these patients. The mean value was 2.15 ± 0.36. The histograms of this group are shown in charts 1 and 2.

TABLE 3.—*Changes in Serum Total Cholesterol During Recovery from Loss of Weight*

Cholesterol, Mg. per 100 Cc.			Weight, Kg.			
First Determination	Second Determination	Deviation	First Determination	Second Determination	Deviation	Interval, Days
77	149	+82	6.1	6.3	0.2	18
85	124	+39	4.9	5.6	0.7	58
85	144	+59	5.0	5.7	0.7	59
87	175	+88	7.4	8.2	0.8	35
93	127	+34	3.7	3.8	0.1	22
99	140	+41	5.2	5.3	0.1	80
100	110	+10	4.5	4.6	0.1	30
102	113	+11	4.9	5.5	0.6	60
103	188	+85	11.8	12.4	0.6	70
104	100	− 4	3.7	4.5	1.8	47
108	141	+33	6.1	6.4	0.3	17
113	140	+27	5.3	5.5	0.2	4
118	154	+36	8.3	8.7	0.4	36
120	131	+11	9.9	10.3	0.4	14
137	127	−10	8.0	8.1	0.1	9
140	186	+46	5.2	5.8	0.6	100+
140	103	−37	5.3	5.7	0.4	20
140	142	+ 2	5.5	5.8	0.3	14
147	194	+47	4.4	7.1	2.7	100+
149	167	+18	6.3	6.5	0.2	11
151	159	+ 8	3.9	4.0	0.1	30
153	222	+79	16.4	18.0	1.6	15
167	197	+30	6.5	6.8	0.3	13
176	207	+31	4.3	4.6	0.3	5

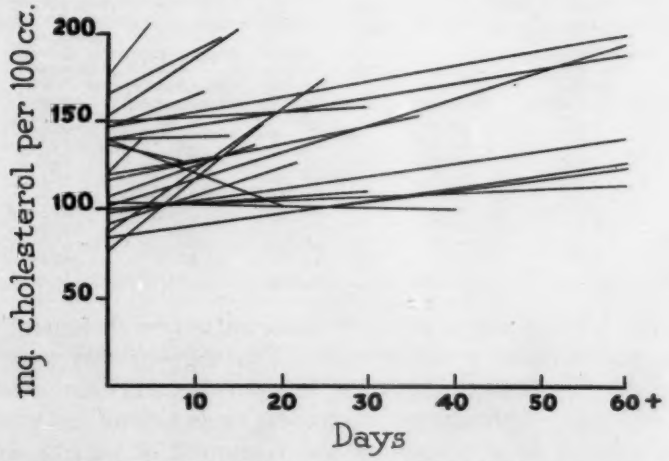

Chart 3.—Rise in level of total cholesterol in the serum during recovery from loss of weight.

It was evident that there was a distinct and statistically significant difference in the values for serum total cholesterol between the normal patients and the patients who were losing weight. The effect of recovery from loss of weight on the total cholesterol content was therefore examined. Twenty-four of the 78 patients had a second determination of cholesterol made while they were regaining weight. The results are shown in table 3 and chart 3. In 21 of the subjects a gain in weight was associated with a rise in the concentration of serum cholesterol;

in only 3 instances was a fall in the cholesterol value recorded. The absolute probability (binomial expansion) that this result could have arisen by chance is of the order of 1 in 7,000. The association in this group between gain in weight and rising cholesterol concentration is therefore highly significant. It was not possible, however, to demonstrate a quantitative relationship between the amount of weight gained and the extent of the rise in serum cholesterol. Correlation coefficients were computed with the changes expressed both on an absolute and on a percentage basis. These coefficients did not differ significantly from zero. This result is in agreement with those of Man and Gildea [5] for adult subjects.

There were only 5 patients who had had two or more determinations of cholesterol made while they were losing weight. Their data are listed in table 4.

It is clear, then, that the total cholesterol content of the serum falls when there is wasting of the body tissues and returns toward normal during the process of recovery. Bruch [3] has likewise shown that there is a fall in the serum cholesterol in obese patients when they are losing weight on a reducing diet.

TABLE 4.—*Changes in Serum Total Cholesterol During Loss of Weight*

Cholesterol, Mg. per 100 Cc.			Weight, Kg.			
First Determination	Second Determination	Deviation	First Determination	Second Determination	Deviation	Interval, Days
123	112	—11	5.0	4.9	—0.1	19
134	82	—52	5.9	5.7	—0.2	12
137	129	— 8	8.4	8.2	—0.2	9
161	153	— 8	16.9	16.4	—0.5	7
189	172	—17	6.5	6.4	—0.1	18

TABLE 5.—*Changes in Ratio of Combined to Free Cholesterol During Change of Weight*

Cholesterol Ratio			Weight, Kg.			
First Determination	Second Determination	Deviation	First Determination	Second Determination	Deviation	Interval, Days
1.26	1.76	+0.50	5.9	5.7	—0.2	16
1.37	2.20	+0.83	6.1	6.3	+0.2	18
1.70	2.23	+0.53	4.4	7.1	+2.7	100+
1.82	2.84	+1.02	4.5	4.6	+0.1	30
2.12	2.71	+0.59	5.0	5.7	+0.7	59
2.39	2.40	+0.01	8.0	8.1	+0.1	9
2.43	2.25	—0.18	6.5	6.4	—0.1	8
2.84	2.14	—0.80	4.6	5.2	+0.6	20
2.86	2.45	—0.41	4.9	5.2	+0.3	14

In chart 2, a histogram of ratios of combined to free cholesterol, the distribution in the malnourished group is wide. This suggests that some factor other than loss of weight influenced the ratio. It is possible, and even probable, that this factor was infection. Although an attempt was made to limit this group to persons without infection, a large proportion was comprised of patients with the celiac syndrome, who are notoriously prone to have hidden foci of infection. However, comparison of the average values for serum cholesterol content and ratio of combined to free cholesterol of the patients with the celiac syndrome with the average values for other patients in the malnourished group failed to show any significant difference.

There were only 9 patients for whom the ratio of combined to free cholesterol had been determined twice. They are listed in table 5. For 5 the ratio rose with

5. Man, E. B., and Gildea, E. F.: Serum Lipoids in Malnutrition, J. Clin. Investigation **15**:203, 1936.

the rise in weight; for 1 both the ratio and the body weight fell. Two had a fall in ratio and a rise in weight; 1, a rise in ratio and a fall in weight. These data give no clear indication of the behavior of the ratio of combined to free cholesterol during wasting of the body tissues.

TABLE 6.—*Anemia Uncomplicated by Loss of Weight, Infection or Evident Hepatic Damage*

Type of Anemia	Age of Patient	Total Cholesterol, Mg./100 Cc.	Combined Cholesterol / Free Cholesterol	Hgb., % of 14.5 Gm./ 100 Cc.
Dietary iron deficiency	16 mo.	79	2.33	20
Dietary iron deficiency	2 yr.	83	2.32	45
Dietary iron deficiency	6 yr.	91	2.47	11
Dietary iron deficiency	12 mo.	98	2.34	25
Dietary iron deficiency	11 mo.	129	....	18
Dietary iron dificiency	4½ yr.	130	....	32
Dietary iron deficiency	18 mo.	135	2.57	30
Dietary iron deficiency	3½ yr.	136	....	29
Dietary iron deficiency	10 yr.	140	2.25	20
Dietary iron deficiency	4½ yr.	170	2.42	38
Dietary iron deficiency	9 yr.	170	2.50	44
Sickle cell	9 yr.	109	2.30	36
Sickle cell	12 yr.	135	2.61	45
Erythroblastic	3½ yr.	97	2.27	53
Erythroblastic	7 mo.	102	1.52	51
Erythroblastic	8 yr.	110	2.15	43
Erythroblastic	3½ yr.	112	2.65	48
Erythroblastic	3 yr.	132	2.20	34
Leukemia	9 yr.	252	2.24	53

TABLE 7.—*Anemia Complicated by Loss of Weight, Infection or Apparent Hepatic Damage*

Type of Anemia	Complication	Age	Total Cholesterol, Mg./100 Cc.	Combined Cholesterol / Free Cholesterol	Hgb., % of 14.5 Gm./ 100 Cc.
Hypoferric	Chronic infection of upper respiratory tract	10 mo.	108	1.46	45
Hypoferric	Chronic infection of upper respiratory tract	9 mo.	117	2.17	40
Hypoferric	Chronic infection of upper respiratory tract	3½ yr.	159	1.94	37
Sickle cell	Chronic infection of upper respiratory tract	16 mo.	131	1.78	28
Sickle cell	Chronic infection of upper respiratory tract	14 mo.	136	1.82	13
Erythroblastic	Loss of weight	5 mo.	68	1.76	40
Erythroblastic	Pyrexia of unknown origin	4 yr.	80	1.54	32
Erythroblastic	Loss of weight	11 yr.	86	1.73	55
Erythroblastic	Chronic sinusitis	5½ yr.	88	1.21	31
Erythroblastic	Loss of weight	7½ yr.	94	2.04	38
Erythroblastic	Pyrexia of unknown origin	12 mo.	109	1.56	45
Leukemia	Infiltration of liver at necropsy	9½ yr.	94	1.70	28
Leukemia	Infiltration of liver at necropsy	4½ yr.	97	1.31	20
Leukemia	Loss of weight	2 yr.	139	1.41	60

TABLE 8.—*Patients with Congenital Hemolytic Icterus*

Patient	Age	Total Cholesterol, Mg./100 Cc.	Combined Cholesterol / Free Cholesterol	Hgb., % of 14.5 Gm./ 100 Cc.
DeL.	10 yr.	80	2.43	20
C., 12/18/34	11 yr.	87	2.49	30
1/31/35	11 yr.	68	1.96	56
2/ 8/35	11 yr.	93	2.30	58
S.	5 yr.	164	2.18	94
F., 12/30/35	9½ yr.	125	2.29	77
1/13/36	9½ yr.	108	2.50	107

THE EFFECT OF ANEMIA

Thirty-eight patients with anemia, whose hemoglobin levels were at or below 55 per cent of 14.5 Gm. per hundred cubic centimeters, had had their serum analyzed for cholesterol concentration. Of these, 18 showed no loss of weight and no evi-

dence of infection or impairment of hepatic function. Their data are grouped in table 6. The mean of the values for total cholesterol is 126.8 ± 40 mg. per hundred cubic centimeters; that for the values of the ratio of combined to free cholesterol 2.32 ± 0.26. Thus the values for total serum cholesterol in patients with severe, uncomplicated anemia differed significantly from the normal. For

TABLE 9.—*Infection Without Loss of Weight (Arranged According to Duration of Infection)*

Age	Diagnosis	Probable Duration	Total Cholesterol, Mg./100 Cc.	Combined Cholesterol / Free Cholesterol	Hgb., % of 14.5 Gm./ 100 Cc.
9 mo.	Infection of upper respiratory tract	1 day	186	2.52	70
2 yr.	Pneumonia	1 day	167	2.54	79
17 mo.	Otitis media	3 days	165	2.04	85
9 mo.	Pneumonia	5 days	102	2.20	69
4 mo.	Pyelitis	5 days	112	1.95	73
2 yr.	Cervical adenitis	6 days	142	1.94	65
2¾ yr.	Pyelitis	1 week	179	1.96	55
1 yr.	Otitis media	1 week	181	1.13	80
6½ yr.	Infection of upper respiratory tract	1 week	162	1.70	80
3 mo.	Infection of upper respiratory tract	1 week+	179	1.96	80
7 mo.	Otitis media	1 week+	177	1.68	87
4½ yr.	Appendicitis	12 days	152	1.85	92
3½ yr.	Pneumonia and measles	2 weeks	176	1.83	59
9½ yr.	Still's disease	4 weeks+	156	1.87	64

TABLE 10.—*Infection with Loss of Weight (Arranged According to Duration of Infection)*

Age	Diagnosis	Probable Duration	Total Cholesterol, Mg./100 Cc.	Combined Cholesterol / Free Cholesterol	Hgb., % of 14.5 Gm./ 100 Cc.
2½ yr.	Pyelitis	1 day	129	2.11	..
13 mo.	Bronchitis	3 days	134	1.74	83
7 wk.	? Sepsis; pneumonia	6 days	108	0.75	77
8 yr.	Pharyngitis	1 week	100	2.08	87
9 mo.	Bronchitis	2 weeks	107	1.92	80
3 mo.	Abscess of lung	2 weeks	133	1.62	65
6½ yr.	Infected hydronephrosis	2 weeks+	140	1.88	75
5 yr.	Abscess of skin	4 weeks+	149	1.78	..
8½ yr.	Pyrexia of unknown origin	5 weeks+	100	1.07	43
17 mo.	Miliary tuberculosis	2 mo.+	63	1.10	57
10 yr.	Pyrexia of unknown origin	3 mo.+	112	1.52	80

TABLE 11.—*Patients with Positive Blood Culture*

Age	Organism	Total Cholesterol, Mg./100 Cc.	Combined Cholesterol / Free Cholesterol	Hgb., % of 14.5 Gm./ 100 Cc.
7 mo.	Bacillus coli	273	0.65	87
2 mo.	Bacillus coli	156	0.22	Not obtained
9 yr.	Staphylococcus aureus	85	0.24	94
4 yr.	Meningococcus	86	1.40	67
7½ yr.	Pneumococcus	111	0.96	71
11 mo.	Pneumococcus	106	1.00	55
3 yr.	Pneumococcus	83	0.99	63
11 mo.	Pneumococcus	97	0.60	Not obtained
5½ mo.	Pneumococcus	109	0.45	74

almost none of the subjects could the duration of the anemia be determined accurately. No correlation was found between the level of total cholesterol and that of hemoglobin. In the majority of patients falling into this group the cause of the anemia was lack of dietary iron, but patients with sickle cell anemia and erythroblastic anemia showed the same phenomenon.

Cholesterol values for patients whose anemia was complicated by loss of weight, infection or impairment of hepatic function are listed in table 7. The number of subjects with each complication was insufficient to warrant statistical analysis.

In the cases of anemia here considered, significantly low values for total cholesterol in the serum were not found unless the level of hemoglobin was below 55 per cent. The exception to this was found in the anemia of congenital hemolytic

TABLE 12.—*Atresia of the Bile Ducts*

(Patients listed according to age)

Patient	Age	Total Cholesterol, Mg./100 Cc.	Combined Cholesterol: Free Cholesterol	State of Nutrition	Hgb., % of 14.5 Gm./100 Cc.	Serum Bilirubin, Mg./100 Cc.
Von S.	3 wk.	216	0.75	Well nourished	71	21.4
GI.	4 wk.	229	0.28	Moderately well nourished	74	15.0
B.	7 wk.	278	0.68	Well nourished; gaining well	86	16.1
E.	3 mo.	190	0.71	Malnourished	74	12.6
O. C.	3½ mo.	169	1.40	Malnourished	78	4.0
D. (10/15/35)	4 mo.	660	0.34	Malnourished	88	5.7
D. (10/22/35)	4 mo.	651	0.34	Losing weight	82	...
N.	4 mo.	151	1.64	Well nourished; alive 2 yr. later.	83	8.8
T.	4½ mo.	143	0.61	Well nourished	58	11.6
G.	6 mo.	175	0.19	Malnourished	50	...
M.	7 mo.	214	0.62	Moderately well nourished	85	8.1
D.	7½ mo.	86	0.33	Losing weight; died same day	65	...
H.	8 mo.	116	0.67	Moderately well nourished	70	19.0
C. (11/ 1/41)	8 mo.	617	0.68	Well nourished	86	...
C. (12/29/41)	9 mo.	545	0.61	Gaining weight	82	...
C. (2/26/42)	11 mo.	895	0.36	Gaining weight	88	...
DeW.	9 mo.	156	0.95	Moderately nourished; gaining weight	62	9.4
H.	18 mo.	193	0.34	Malnourished	50	...

TABLE 13.—*Acute Hepatitis*

(Plus 1 Case of Acute Phosphorus Intoxication)

Patient	Age	Diagnosis	Date	Total Cholesterol, Mg./100 Cc.	Combined Cholesterol: Free Cholesterol	Weight	Temperature, F.	Hgb., % of 14.5 Gm./100 Cc.	Icterus
A. S.	2¼ yr.	Acute catarrhal jaundice	11/24/34	145	2.28	No change	101.6	70	None
			12/ 4/34	171	0.51		N.	70	Faint
			12/ 7/34	375	0.20		N.	70	Cleared
			12/14/34	343	0.65		N.	..	Cleared
E. S.	2¼ yr.	Acute catarrhal jaundice	11/24/34	494	0.20	No change	100	82	Present
			12/ 4/34	250	0.88		N.	..	Clearing
			12/ 7/34	295	2.84		N.	..	Cleared
			12/14/34	183	2.68		N.	..	Cleared
M.	6½ yr.	Acute catarrhal jaundice	11/13/34	198	0.13	16.9 Kg.	101.6	100	Severe
			11/20/34	133	0.06	16.4 Kg.	104	75	Severe
			12/ 5/34	130	0.41	15.7 Kg.	104	63	Clearing
			12/18/34	220	2.31	16.4 Kg.	N.	67	Almost clear
V.	11 yr.	Acute catarrhal jaundice	12/ 9/35	218	0.87	.....	N.	94	Present
			12/20/35	272	2.67	.....	N.	..	Cleared
T.	14 mo.	Acute catarrhal jaundice	.....	109	0.21	Slight loss	103	46	Present
G.	12 yr.	Acute catarrhal jaundice	.....	169	2.10	No loss	N.	..	Almost clear
F.	8 yr.	Acute catarrhal jaundice	.....	151	0.53	No loss	100	..	Present
P.	7 yr.	Acute catarrhal jaundice	.....	169	0.71	Gaining	N.	81	Clearing
L.	9 yr.	Acute catarrhal jaundice	.....	229	0.74	.....	N.	..	Present
S.	8 yr.	Acute catarrhal jaundice	.....	237	0.26	.....	..	..	Present
S.	12 yr.	Pneumonia with hepatitis	12/18/34	255	0.85	51.0 Kg.	N.	98	Present
			12/22/34	250	0.92	49.7 Kg.	N.	..	Present
T.	1¾ yr.	Acute phosphorus intoxication	5/ 8/36	239	2.72	.....	103	77	Absent
			5/13/36	132	0.49	.....	104	..	Present
			5/15/36	101	0.29	.....	105	..	Present

icterus. Here the level of total cholesterol was low regardless of the level of hemoglobin. No satisfactory explanation for this was found. There was no loss of weight and no evidence of infection or obvious hepatic dysfunction in this group. The values are listed separately in table 8.

THE EFFECT OF INFECTION

From the data at hand it was difficult to evaluate the effect of infection uncomplicated by loss of weight, anemia or obvious hepatic damage. Many of the determinations were made on the day of admission to the hospital, when there was no reliable record of previous change in weight. From a large mass of material only 14 cases in which the proof of no recent loss of weight was adequate were selected. These are listed in table 9. The average value for the total cholesterol of the serum was 159.7 ± 31; that for the ratio of combined to free cholesterol, 1.94 ± 0.35. Reliable evidence of loss of weight was afforded by 11 patients who are listed in table 10. Here the average value for total cholesterol was 115.9 ± 24 mg. per hundred cubic centimeters, and that for the ratio, 1.60 ± 0.44. The average for each group is significantly lower than the normal for both the total cholesterol and the ratio. The average duration of the infection was much longer in the group

TABLE 14.—*Nonobstructive Cirrhosis, Laennec Type*

Patient	Age	Total Cholesterol, Mg./100 Cc.	Combined Cholesterol / Free Cholesterol	Weight Change	Infection	Hgb., % of 14.5 Gm./100 Cc.
H. 9/ 1/36	7½ yr.	192	2.85	Gaining	None	74
11/13/36	7½ yr.	200	2.58	Gaining	None	..
3/ 8/36	8 yr.	163	2.94	Gaining	None	..
4/14/37	8 yr.	179	2.48	Gaining	None	..
C.	2 yr.	207	1.81	Gaining	None	80
T.	10 yr.	241	1.94	Gaining	None	93
B.	4½ yr.	175	3.14	Slight loss	None	86
S.	6½ yr.	137	2.57	Gaining	None	95
S.	9 yr.	136	2.63	Gaining	None	..
M.	8 mo.	100	0.62	Pronounced loss	Pyrexia of unknown origin	80
Be.	2 yr.	199	3.06	Gaining	None	55
Bo.	8 yr.	419	1.79	Gaining	Upper respiratory tract for 1 week	100
M.	10 yr.	184	1.24	Losing	Upper respiratory tract for 2 weeks	81
	10½ yr.	214	1.95	Gaining	None	..
H.	1½ yr.	339	1.38	Losing	Pyrexia of unknown origin	77
A. 12/ 1/36	5½ yr.	294	2.37	Gaining	None	60
1/23/40	9 yr.	347	0.40	Slowly gaining	None	87
5/20/41	10 yr.	205	0.26	Slowly gaining	Upper respiratory tract for 3 weeks	73

with loss of weight than in the group without that complication. Therefore, a comparison between these groups is not justified. Stoesser [6] has adequately discussed the effect of infection on the concentration of serum cholesterol.

Nine patients with positive blood cultures had a rather wide range of values for serum total cholesterol (122.0 ± 60 mg. per hundred cubic centimeters), but had uniformly low values for the ratio of combined to free cholesterol (0.73 ± 0.14). They are listed in table 11.

THE EFFECT OF DISEASE OF THE LIVER

The 36 patients with clearcut disease of the liver fell into three groups. The first group was composed of 15 patients with congenital atresia of the bile ducts. For each the diagnosis was confirmed at operation or at necropsy. The data for this group are presented in table 12. The values for serum total cholesterol varied widely. No good explanation for the large differences in values was found. The level did not appear to be consistently influenced by age, state of nutrition, level

6. Stoesser, A. V.: Altered Lipid Metabolism in Acute Infections of Infants and of Older Children, Am. J. Dis. Child. **56**:1215 (Dec.) 1938.

of hemoglobin or level of serum bilirubin. The cholesterol ratio was uniformly low, with an average of 0.64 ± 0.38.

Ten patients had acute catarrhal jaundice. For these the ratio of combined to free cholesterol closely paralleled the clinical course of the disease, falling to low levels during the acute stage and returning promptly toward normal with fall of temperature and clearing of clinical icterus. The data for A. S., table 13, are of particular interest, since they show that the ratio of combined to free cholesterol may be normal early in the course of the disease and then drop to low levels as damage to the liver becomes more pronounced. The data for this group are listed in table 13 together with those for 1 patient with acute hepatitis complicating pneumonia and 1 with acute phosphorus intoxication.

Table 14 gives the data for 11 patients with nonobstructive cirrhosis of the Laennec type. The values for serum total cholesterol were within or somewhat above the normal range save in one instance in which there was considerable loss of weight. With the single exception of that of subject A. on Jan. 23, 1940, values for the ratio of combined to free cholesterol did not fall significantly below the normal unless there was superimposed infection. Thus this ratio appears to be a poor index of hepatic function in nonobstructive cirrhosis of the Laennec type.

SUMMARY

Examination of the values for cholesterol concentration in the serum of 417 normal persons from 1 month to 14 years of age showed no systematic trend with advancing age. The ratio of combined to free cholesterol was determined in 344 instances and also showed no significant trend. The mean value for the total cholesterol was 205.7 ± 38 (standard deviation) mg. per hundred cubic centimeters; the mean value for the ratio was 2.58 ± 0.29.

In 78 patients with wasting of the body tissues there was a significant lowering of the total cholesterol of the serum. The mean value was 123.0 ± 29 mg. per hundred cubic centimeters. There was a significant return toward normal during recovery from loss of weight. The ratio of combined to free cholesterol was also lowered but to a less degree. The mean value was 2.15 ± 0.36. It is postulated that this lowering was largely due to undiscovered infection in this group of patients.

In 18 patients with severe uncomplicated anemia there was a significant lowering of the total cholesterol. The mean value was 126.8 ± 40 mg. per hundred cubic centimeters. The mean value for the ratio of combined to free cholesterol, 2.32 ± 0.26, does not represent a significant lowering.

In 25 patients with infection, 9 patients with positive blood cultures, 10 patients with acute catarrhal jaundice and 15 patients with atresia of the bile ducts there was a significant lowering of the ratio of combined to free cholesterol. It is inferred that this lowering is due to acute damage to the hepatic cells.

In 11 patients with nonobstructive cirrhosis of the Laennec type there were no deviations from normal of the total cholesterol, and only one deviation of the ratio of combined to free cholesterol from normal, which could not be explained by the presence of some secondary complication.

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DIAGNOSIS OF JUVENILE PSYCHOSIS

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The problem of juvenile psychosis has only in recent years become a serious concern of the practicing physician. In the past, even psychiatrists neglected the juvenile psychoses on the prevailing assumption that definite mental abnormalities developed only during the postadolescent and adult years. During recent years, however, intensive studies of children with severe and persistent behavioral and personality changes have shown that a large number of the psychotic conditions which are first diagnosed during the postadolescent and adult years in reality originate during childhood. The conditions of many children are erroneously diagnosed as simple behavior problems, and their psychotic conditions are overlooked.

The majority of juvenile psychotic subjects have schizophrenia, but the symptoms are usually different from those of schizophrenia in an adult. This is due essentially to their intellectual, emotional and experiential immaturity. Juvenile psychotic patients rarely have well defined delusions, probably because they have not as yet acquired a definite system of values and their symbolism is not as yet patterned. In spite of the rarity with which hallucinations and delusions occur, which form important criteria for the diagnosis of adult mental abnormalities, the symptoms of a psychotic child are sufficiently specific that a diagnosis of juvenile psychosis can be made fairly easily.

This paper is the report of a study of 35 children whose condition was diagnosed as psychotic and who were observed for periods ranging from two to ten years. A detailed history of the behavioral development of each child was obtained from its parents and teachers. The progress of these children under therapeutic conditions was also observed. Ten of the 35 children were committed to state hospitals for the insane by the time they were 20 years old, and it is probable that several others will have been committed when they are that age. The majority of the 35 patients were intellectually normal during their infancy and early childhood, and no one in the family suspected at that time that they were different from other children. In 26 the mental abnormalities developed in a recognizable form when they were between 11 and 13 years old, and in the remainder, when they were 10 years old or younger.

In all but 1 case the parents stated that the behavior of the child was good before he manifested the nervous or other aberrant activities. Indeed, the majority of the subjects were model, well behaved children, who gave their parents and their teachers no trouble. In most of the cases the parents wondered about their child's development only because he did not make good progress in school or when his symptoms of excessive seclusiveness, mannerisms and (in several instances) hallucinatory behavior developed. A similar observation of the childhood behavior of psychotic adults was made by Bowman,[1] who found after consultations with

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1. Bowman, K.: A Study of the Pre-Psychotic Personality in Certain Psychoses, A. Research Nerv. & Ment. Dis., Proc. **14**:180-210, 1933.

relatives and friends that these patients had been considered model children. They were relatively uncommunicative and withdrawn and rarely showed any delinquent or other antisocial behavior.

The following were the most typical and consistent symptoms of the juvenile psychotic patients:

1. Seclusiveness and social withdrawal. The seclusiveness was different from the behavior of shy normal children who because of their feelings of inadequacy or inferiority are unable to adjust adequately to other children. The psychotic children when placed with other children seemed to be out of contact, although they did not necessarily attempt to escape from them.

2. Emotional rigidity. This, usually one of the most frequent symptoms, began early in the psychotic condition and became increasingly severe. The emotional rigidity varied. One 13 year old boy invariably talked of his pleasant experiences with other children, with his teachers, with his food and with his living arrangements. Almost every experience he had was reported by him as "magnificent" and "wonderful." On one occasion he was telling the interviewer that the weather was magnificent because there was always sunshine, but when he was told to look out of the window at the rain he said that it was magnificent anyway because it was raining. Another boy of the same age appeared depressed and at no time during a period of six months did he change his emotional tone.

3. Varying degrees of personality dissociation. The degree of personality dissociation was not related to the severity of the other symptoms or to the age of the patient. A child of 9 years who was still able to adjust himself fairly adequately was dissociated, whereas a 13 year old child who had a great deal of difficulty because of emotional disturbances was only slightly dissociated. Mental dissociation usually manifested itself in defective orientation to other children, various linguistic dissociations and concentration on a given activity to the exclusion of all other activities. For example, one 11 year old boy followed the directions of his teacher in making a drawing but when told to stop at the end of thirty minutes said that he was unable to stop and continued for more than an hour after the other children had finished their work.

4. Unusual attention to detail. In the case of one boy the attention to detail showed itself in repetitive writing. For instance, when he was asked to write his name he wrote it more than fifty times and explained the repetition by stating that he wanted to write it carefully. Another boy who was drawing a house made an outline and elaborated on three windows, inserting more than thirty windowpanes, but forgot to insert a door in his finished drawing.

5. Excessive daydreaming and vivid phantasy. In a number of children the phantasy was so vivid that they reacted to imaginary companions and conditions as if they were realities. One boy had two imaginary companions whom he named and to whom he addressed questions, although he was able to admit that he could not see them and that they were imagined. Another boy had phantasies of being in church and prayed to himself frequently. He stated that the church scenes were imaginative but nevertheless satisfying.

6. Differential intellectual deterioration. Although the intelligence of the psychotic children did not deteriorate in terms of the intelligence quotient, given capacities did show deterioration. The most common deterioration was in judgment and occasionally in some subject matter, such as arithmetic or spelling. The judgment of the psychotic children seemed to become poorer. The discrepancy between the response to items on the tests which required judgment and their actual judgment in everyday behavior was frequently marked.

7. Manneristic behavior. This occurred in more than 50 per cent of the children. The mannerisms were expressed in repetitive acts. One boy, for example, stated that he had a compulsive feeling to tap on a cup or dish and that the tapping gave him a feeling of pleasure. Another boy made a dancing motion whenever he sat down and, although he recognized the action as abnormal, was unable to stop it. A third boy stated that he had a constant desire to perform an act twice. For example, he always buttoned his clothes twice, opened a door twice or sat down twice before he could sit still in a chair.

Physiologic tests of activity of the autonomic nervous system revealed specific correlates of the psychotic condition. The patients were examined by photopolygraphic methods, which recorded blood pressure, respiratory rate, heart rate and changes in the electrical resistance of the skin. Changes of cutaneous electrical resistance were found to be most significant. In a normal child electrical resistance of the skin decreases rapidly immediately after a sensory or an emotionally provoking stimulus is given, and the return to normal is also fairly rapid. In a neurotic child the responses are greater and more irregular than in a normal child. In the psychotic children, however, the responses were extremely slight, even with intense stimulation. The rigidity of activity of the autonomic nervous system was closely related to the severity of the psychotic condition. The children with the more severe psychotic conditions showed the greater rigidity of the autonomic nervous system.

Electroencephalographic records were made of the children under varying conditions. The brain waves were normal and showed a normal frequency and rhythm when the child was in a resting state. When a strong sensory stimulus was given, there was only a slight change in the alpha rhythm and also an almost immediate return to normal. In a normal child the return is gradual and in a neurotic child it is extremely slow. The immediate return to normal indicates that the psychotic child is not significantly disturbed emotionally by stimuli which affect a normal child. The threshold is high both to sensory and to verbal stimuli. The high physiologic threshold and the momentary responses correlate with the unresponsiveness of a psychotic child to many social situations.

The following are brief résumés of the observations on several psychotic children.

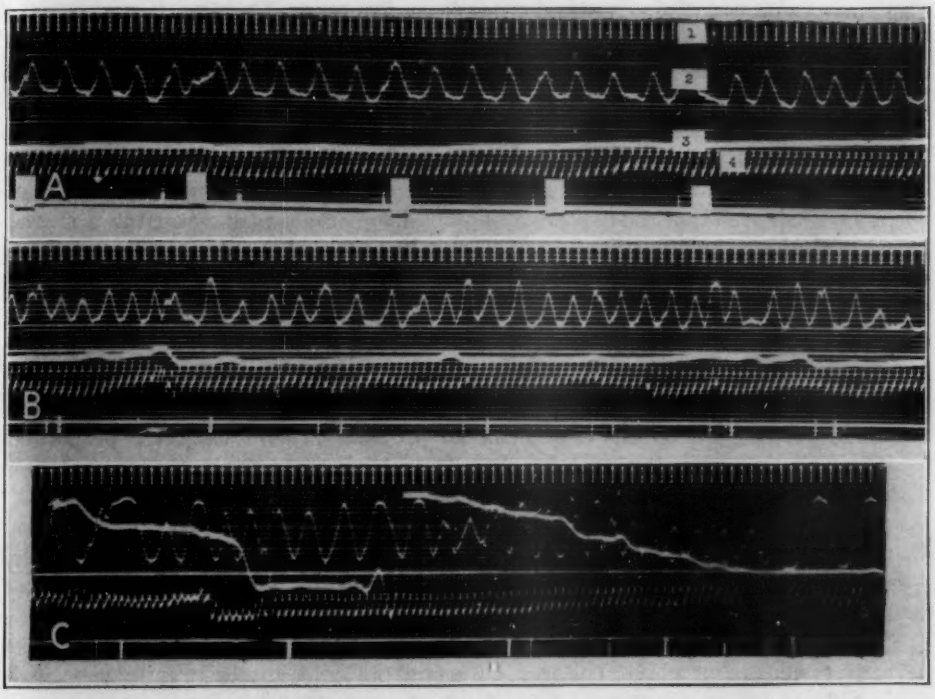
REPORT OF CASES

CASE 1.—J. M., a boy of 12 years, had been excluded from school because the teachers complained of his nervous and peculiar behavior. The parents stated that during the last two years he had become seclusive and irritable. During his early childhood, he had seemed to be happy and well adjusted and had never given his parents any difficulty or annoyance. They had also noticed that he had peculiar "spells," consisting of remaining motionless in a rigid position for thirty minutes or more and when questioned stating that he was merely "thinking." Examination showed a boy who was emotionally rigid. He did not smile, nor did he seem interested in the conversation. He stated that he felt fine but did not want to go to school because the teacher bothered him. He showed a great deal of perseveration in his verbal responses. He did not respond to questions and statements which usually result in strong emotional reactions by normal children. Intelligence tests showed him to have average intelligence, but he was defective in judgment. He seemed self contained and uninterested in his surroundings and showed no insight into his condition. He was apparently seriously dissociated from reality.

CASE 2.—R. F., a boy of 13 years, was brought for examination some nine months after his exclusion from a public school. The teachers complained about his making queer noises and talking at length about irrelevant subjects. His parents stated that at the age of 10 years he had invented imaginary companions and apparently conversed with them. The boy had no friends and preferred to play with toys or to listen to the radio. On examination he was found to be undernourished and underdeveloped; his hands were moist and his pupils enlarged. He refused to talk about himself but did speak about his imaginary companion, whom he

called "Renol." This imaginary person was somewhat older than he, large and strong and able to do many things. He was emotionally apathetic and seemed to be uninterested in most subjects in which children of his age show a great deal of interest. The cutaneous electrical resistance was low, and stimuli such as loud noises, pinching of the skin or verbal accusations caused only slight changes. An electroencephalographic record showed a normal rhythm and amplitude of the alpha waves with little change when sensory stimuli were applied.

CASE 3.—H. C., a girl of 8 years, had not conversed with any one but her parents for about three years and seemed to have many fears. She was restless and irritable and was unable to fall asleep unless she had a light in her room or her mother stayed with her. Observation showed her to be thoroughly uninterested in the activities of other children or in their advances toward her. She failed to make any friends with children of her own age and usually played with toys. She seemed to be suspicious of adults as well as children and responded antagonistically to any physical contact. She gradually responded to urging and, when she became responsive in the interview, talked about "funny" people who wanted to



Photopolygraphic tracings from normal and abnormal children (*1*, time line; *2*, respiratory curve; *3*, cutaneous galvanic response; *4*, heart rate and blood pressure; the tracings read from right to left). *A*, tracing from a psychotic boy of 13 years. Note the unchanged curves for respiration, blood pressure and cutaneous resistance when stimuli are applied. *B*, tracing from a normal 12 year old boy. Note the return to normal after stimulation. *C*, tracing from neurotic boy of 12 years. Note the rapid and irregular changes when stimuli are applied.

harm her and explained her previous refusal to talk as a fear of telling anything about herself because others would then be mean to her.

CASE 4.—L. B., a boy of 9 years had attended school for only six months. He was described as restless and irritable. He lacked concentration and refused to pay attention to the teachers. The teachers had believed that he was so defective mentally that they could not keep him in the first grade. Since then he had been given school work at home, but his tutors reported that he was unable to learn any school subjects. On examination he was extremely restless, asked many irrelevant questions and repeated the questions even after careful answers were given. He seemed to pay no attention to his questions or to the answers.

He talked constantly and frequently rhymed words in the process of asking a question. When placed with other children, he showed similar behavior, asking one child and then another all sorts of questions. When he was examined physically, he asked the nurse whether he was 80 pounds "tall" and without waiting for an answer asked another entirely unrelated question. Although no verbal statement could be obtained from him regarding his emotional reactions, he seemed to be fearful but in spite of his fears continually smiled. Intelligence tests showed that he had an average intelligence quotient, although many items in the test had to be repeated to him because of his poor concentration.

Hallucinatory experiences were found in only 1 case, in which the child reacted as if he had visual hallucinations. The delusions of the children were relatively unorganized and appeared only in relation to their attempts to adjust to other children and adults. This may be due to the fact that children have not as yet developed a complete symbolic world and their thinking is generally directed in terms of concrete situations rather than of abstractions. Thus, the delusional formation is necessarily exceedingly simple and naive.[2] The fact that organized delusions and hallucinations are only rarely found in these children accounts for the frequent failure to make a specific diagnosis of a psychosis. This probably also accounts for the few commitments to state institutions, although most psychiatrists hesitate to send a seriously disturbed child to a state institution. The diagnosis of juvenile psychosis is also complicated by the fact that the symptoms of mentally defective children are often confused with the symptoms of psychotic children.[3] Richmond [4] showed that the psychosis of a child sometimes is diagnosed as a mental defect. She suggested that careful intelligence tests should be performed on children who are suspected of being mentally defective but who show behavior which simulates a psychotic condition.

SUMMARY

The frequency of juvenile psychosis is probably much greater than is generally believed. Physicians often fail to make a diagnosis of a psychotic condition because they tend to make a diagnosis of a "behavior problem" when a child acts peculiarly.

A psychotic condition must be considered a disease rather than a behavior disturbance even when it occurs in a child.

A psychosis must be suspected if the personality of a child changes to one characterized by seclusiveness, emotional rigidity and poor school performance, especially when there is evidence of mental dissociation, such as compulsive and manneristic behavior.

There is a significant increase in the threshold of the functions of the autonomic nervous system in psychotic children. Certain physiologic measures may be used to confirm or negate the presence of a psychosis in a child.

1365 East Sixtieth Street.

2. Potter, H. W.: Schizophrenia in Children, Am. J. Psychiat. **12**:1254-1270, 1933.
3. Greene, R. A.: Conflicts in Diagnosis Between Mental Deficiency and Certain Psychoses, Proc. Am. A. Ment. Deficiency **57**:127-148, 1933.
4. Richmond, W.: The Dementia Praecox Child, Am. J. Psychiat. **11**:1153-1159, 1932.

IMMUNITY TO TETANUS INDUCED BY A THIRD DOSE OF TOXOID TWO YEARS AFTER BASIC IMMUNIZATION

BASED ON A STUDY OF THIRTY-ONE ALLERGIC CHILDREN

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In my previous study [1] on the appearance of tetanus antitoxin in the blood serum following two injections of 0.5 cc. each of combined alum-precipitated diphtheria and tetanus toxoids, special reference was made to the influence of the interval between injections. It was also shown that 94.6 per cent of a group of 186 allergic children attained a protective level of tetanus antitoxin, the critical level being placed at 0.01 American unit of antitoxin per cubic centimeter of blood. In a subsequent study [2] a third, or "booster," injection of 0.5 cc. of the combined alum-precipitated toxoids was given to 65 of the 186 children used in the first report. Nine of these 65 children had failed to attain adequate immunity after two doses of the combined alum-precipitated toxoids. The "booster" dose was administered from three to fifteen months after the completion of primary immunization with two doses of combined toxoids. The booster dose of the combined toxoids was followed in all instances by an adequate tetanus antitoxin titer, which was higher and lasted for a much longer period than that which followed the second injection, even though the corresponding titer obtained within one month of the third injection was the same or less.

In this communication, I am reporting the results of a study comparing the initial maximum tetanus antitoxin levels and the corresponding titers ranging up to two years after the administration of the third and the second doses of toxoid to 31 of the 186 children used in the study described in the first report. All of these 31 children attained adequate immunity after two doses of the combined toxoids. These children were divided into two groups. One group of 18 children was given a "booster" dose of 0.5 cc. of the combined alum-precipitated diphtheria and tetanus toxoids, and the second group, of 13 children, was given a "booster" dose of 0.5 cc. of alum-precipitated tetanus toxoid alone. The creation of these two groups served a definite purpose which will be explained later. Since there was no appreciable difference in the immunity to tetanus induced by either the combined toxoids or the tetanus toxoid alone, the 31 children comprising this series were therefore treated as a single group for purposes of recording the antitoxin titers.

F. G. Jones, of the Lilly Research Laboratories, gave technical assistance in this study.

From the Children's Allergy Clinic, Mount Sinai Hospital, Dr. Murray H. Bass, Director of the Department of Pediatrics.

The preparations of combined alum-precipitated diphtheria and tetanus toxoids and alum-precipitated tetanus toxoid used in this study were furnished by Eli Lilly & Co.

1. Peshkin, M. M.: Immunity to Tetanus Induced by Combined Alum-Precipitated Diphtheria and Tetanus Toxoids, Based on a Study of One Hundred and Eighty-Six Allergic Children, Am. J. Dis. Child. **62**:9 (July) 1941.

2. Peshkin, M. M.: Immunity to Tetanus Induced by Combined Alum-Precipitated Diphtheria and Tetanus Toxoids, Based on a Study of Sixty-Five Allergic Children Given a Third or "Repeat" Dose, Am. J. Dis. Child. **62**:309 (Aug.) 1941.

MATERIALS AND METHODS

A total of 194 blood serums titrated for tetanus antitoxin were obtained from the 31 allergic children after the "booster" injection of 0.5 cc. of the alum-precipitated toxoid (either combined diphtheria and tetanus toxoids or tetanus toxoid alone). This dose was administered two years after completion of the basic immunization with two 0.5 cc. doses of the combined toxoids. One hundred and fifty-nine blood serums had been titrated after the first two injections.

TETANUS ANTITOXIN TITERS AFTER THE SECOND AND AFTER THE THIRD, OR "BOOSTER," DOSE OF ALUM-PRECIPITATED TOXOIDS

Examination of the data reveals that for 31 patients titers determined after the second dose of toxoid were available for study with the 119 obtained at intervals of from one month to two years after the third dose. The antitoxin value after the third dose of the toxoid was higher in 112 of the 119 instances, lower in 1 and the same in 6. After the third dose the average increase in the antitoxin value was six times more than the average corresponding titers after the second dose. In the 1 instance in which the antitoxin titer was lower after the third dose of toxoid when compared with the corresponding titer after the second dose, the antitoxin values were 0.003 and 0.017, respectively.

From the data on 25 children it was found that when the initial tests were done within two months of giving the toxoid, at which time the comparative tests showed the antitoxin values following the respective third and second doses to be higher after the third dose, then the tests performed two years later revealed not only that the drop of the titer was retarded after the third dose but that the antitoxin values were also distinctly higher (for a ratio of 10: 1 or for an average antitoxin titer of 0.208 unit as compared with 0.021 unit).

ANTITOXIN TITER WITHIN ONE MONTH OF THE "BOOSTER" DOSE OF TOXOID AND THE CONTROL TITER

Data from which to determine the effect of the third, or "booster," dose of toxoid on the antitoxin response, with reference to the antitoxin titer obtained after the second and immediately preceding the third dose of toxoid, were available for 31 patients. These patients were divided into two groups. Group 1 consisted of 7 children who had an adequate antitoxin level soon after the second dose of toxoid but whose titers some months later dropped to the level of 0.003 unit per cubic centimeter of serum. After the third dose of toxoid the titers ranged from 1 to 2 units of antitoxin, or an average of 1.4 units, per patient. The increase in titer was from 333 to 666 times, or an average of 476 times more than the control titer, of 0.003 unit.

Group 2 consisted of 24 patients who also had an adequate antitoxin response soon after the second dose of toxoid but whose subsequent titers, obtained some months later, though lowered, remained above the critical level of protection against tetanus. After the third dose of toxoid the titers of these patients ranged from 0.5 unit to 5 units of antitoxin, or an average titer of 2.4 units. The increase in the titer ranged from 22 to 217 times, or an average of 104 times, more than the average control titer, of 0.023 unit of antitoxin.

An analysis of the foregoing figures and of the other data indicated that the antitoxin values obtained within one month after the administration of a third dose of toxoid varied according to the antitoxin level present immediately preceding the booster dose. When the titer dropped to the inadequate level (0.003 unit of antitoxin) subsequent to being adequate (0.01 unit or more of antitoxin) after two doses of toxoid, then the average titer following a third dose rose to 1.4 units of

antitoxin. When the titer was always maintained at the adequate level after two doses of toxoid, then the titer following a third dose reached the highest antitoxin value, the average being 2.4 units of antitoxin. A comparison of the foregoing antitoxin values with those obtained following a third dose of toxoid given from three to fifteen months after the second injection [2] shows the antitoxin values reported in the present study to be higher, for a ratio of 1.5 : 1.

TIME OF OCCURRENCE OF THE MAXIMUM ANTITOXIN RESPONSE

To determine the maximum antitoxin response following the third dose of toxoid, 2 or more tests were done within three months of the injection on the 31 patients comprising this study.

Thirty patients were tested seven days after the third dose; 1 was tested within one month of the third dose. All 30 patients had 0.2 unit or more of antitoxin per cubic centimeter of serum, as follows: 0.2 unit, 2 children; 0.5 unit, 7 children; 1 unit, 4 children; 2 units, 13 children, and 5 units, 4 children. These results indicated that significantly adequate tetanus antitoxin levels were attained seven days after the injection of a booster dose of 0.5 cc. of either the combined alum-precipitated diphtheria and tetanus toxoids or the alum-precipitated tetanus toxoid alone by all of the children treated two years after the completion of basic immunization with two doses of toxoid. The antitoxin level ranged from 0.2 to 5 units in all of the children treated. For 20 of the patients the antitoxin titer was at its maximum seven days after the administration of the toxoid, while for the remaining 10 patients the titer was at its maximum one month later.

The 1 patient first tested within one month of receiving the third dose of toxoid two years after basic immunization had an antitoxin level of 1 unit per cubic centimeter of serum. The antitoxin titer remained the same two months later.

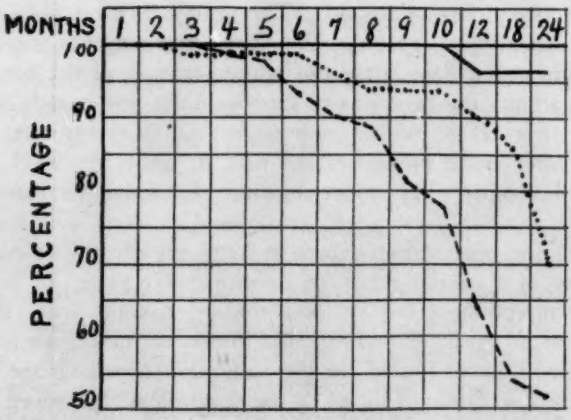
All of the foregoing observations confirm more vividly the results recorded in the preceding paper of a similar study on a comparable group of 38 patients who received the third injection of 0.5 cc. of combined toxoids from three to fifteen months after the second dose. However, in addition to the higher antitoxin values obtained after a third dose of toxoid for the children comprising the present series, adequate titers were also attained by all of the children within seven days after the administration of toxoid. In a comparable group of children reported on in the preceding paper, adequate titers were attained by all the children within one month after the third dose of toxoid. For the majority of the children in this and the comparable series the antitoxin titer was at its maximum level on the seventh day after the toxoid was administered.

RATE OF DECLINE OF THE ANTITOXIN TITER FROM AN ADEQUATE TO AN INADEQUATE LEVEL

All of the 31 children comprising the present study acquired adequate tetanus antitoxin levels within one month after the third, or "booster," dose of toxoid administered two years after the second injection. The relation between the percentage of children who showed a drop of antitoxin titer from an adequate to an inadequate level and the number of months required for the titer to drop to the inadequate level is shown in the chart. For purposes of contrast, there is also shown in the chart one antitoxin curve constructed from data for a comparable group of 51 children who received a third dose of combined toxoids from three to fifteen months after the second injection and another antitoxin curve for a comparable group of 129 children who received only two doses of combined toxoids.

It was previously stated that an antitoxin titer which dropped to the inadequate level (0.003 unit per cubic centimeter of serum) after a dose of toxoid was maintained at this residual level for at least two years. For this reason it was found unnecessary to retest all of these children within the period covered by this study. Nevertheless, retests on the large majority of these children were carried out in order to detect any sharp rise of antitoxin titer which might possibly follow a "natural" stimulus. No such a rise of antitoxin titer was observed. Perusal of the results of the 191 tests after the third injection into the 31 children of this study revealed that the titers of all the children fell progressively from their initial maximum levels. Twenty-five of these children were available for testing two years later.

Examination of the chart shows that for the first ten months after the third dose of toxoid was given two years after basic immunization 100 per cent of this group of 25 children maintained adequate immunity. One, one and one-half and two years after receiving the injection of toxoid 96 per cent of the children had adequate antitoxin levels. In contrast, the percentages of the 51 children who maintained adequate immunity for corresponding periods after the third dose of



Percentages of 31 allergic children (solid line) who had achieved adequate immunity to tetanus (0.01 unit or more of antitoxin per cubic centimeter of blood serum) within one month after a third, or "booster," dose of either combined alum-precipitated diphtheria and tetanus toxoids or alum-precipitated tetanus toxoid given two years after basic immunization and of a parallel group of 51 allergic children (dotted line) who received a booster dose of combined toxoids from three to fifteen months after immunization. There is also shown the percentages of a third group of 129 allergic children (broken line) who had adequate antitoxin levels after basic immunization with two doses of the combined toxoids and who maintained adequate antitoxin titers for a varying number of months after immunization.

toxoid given from three to fifteen months after the second dose were 94, 90, 86 and 70. The percentages of the 129 children who maintained adequate immunity for corresponding periods after the second dose of toxoid were 77.5, 64, 54 and 52. Moreover, the adequate antitoxin levels in the latter two groups of children fell below the 100 per cent level some months prior to ten months after the last doses of toxoid.

It is obvious from the curves in the chart that a definitely greater percentage of children who received a third injection of toxoid two years after the completion of basic immunization with two doses had adequate immunity to tetanus one, one

Maximum Tetanus Antitoxin Titer of Allergic Children and Titers Obtained Less Than Two Years, When the Titer Dropped to 0.003 Unit of Antitoxin Per Cubic Centimeter of Blood Serum, and Two Years After the Second and Third Injections of Combined Alum-Precipitated Diphtheria and Tetanus Toxoids *

Maximum Antitoxin Titer	Patients		Antitoxin Titer, Units per Cc. of Serum, After Injection of Toxoid															
			Less Than Two Years 0.003 †		Two Years													
					0.003		0.01 ‡		0.05		0.1		0.2		0.5		0.01 or More	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
After Second Dose																		
0.01 ‡	12	9	11	92	0	0	1	8	0	0	0	0	0	0	0	0	1	8
0.05	16	12	14	87	0	0	2	13	0	0	0	0	0	0	0	0	2	13
0.1	19	15	11	58	1	5	5	26	2	11	0	0	0	0	0	0	7	37
0.2	42	32	18	43	2	5	19	46	1	2	1	2	1	2	0	0	22	52
0.5	22	17	3	14	0	0	9	41	6	27	3	14	1	4	0	0	19	86
1.0 or more	18	15	2	11	0	0	5	28	5	28	4	22	2	11	0	0	16	89
Total	129	100	59	46	3	2	41	32	14	11	8	6	4	3	0	0	67	52
After Third Dose (Given Three to Fifteen Months after Second Dose)																		
0.01 ‡	1	2	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.1	4	8	1	25	1	25	2	50	0	0	0	0	0	0	0	0	2	50
0.2	10	20	4	40	5	50	1	10	0	0	0	0	0	0	0	0	1	10
0.5	14	27	0	0	2	14	8	57	3	22	1	7	0	0	0	0	12	86
1.0 or more	22	43	1	4	0	0	6	27	7	32	5	23	3	14	0	0	21	95
Total	51	100	7	14	8	15	17	33	10	20	6	12	3	6	0	0	46	90
After Third Dose (Given Two Years after Second Dose)																		
0.5	1	4	0	0	0	0	0	0	1	100	0	0	0	0	0	0	1	100
1.0 or more	24	96	1	4	0	0	2	8	3	13	2	8	12	50	4	17	23	96
Total	25	100	1	4	0	0	2	8	4	16	2	8	12	48	4	16	24	96

* Data are included only for those children for whom titrations were performed within forty days of the injection of toxoid. Data for the 129 children given two doses and for the 51 children given a third injection from three to fifteen months after the second dose were obtained in previous studies (footnotes 1 and 2). Twelve of the 25 children who received a third injection two years after the second dose were given tetanus alum-precipitated toxoid alone. All percentages are approximate.

† Data for patients with an antitoxin titer of 0.003 unit less than two years after immunization are included because such titers persist at this level for at least two years.

‡ Patients with antitoxin levels of 0.017 and 0.025 unit are grouped with those having a titer of 0.01 unit.

and one-half and two years later than either those given a third dose of toxoid from three to fifteen months after basic immunization or those given basic immunization only. Furthermore, of the three groups of children studied over the various intervals for two years, the group of children given only two doses of toxoid showed the lowest percentage of adequate antitoxin levels.

INITIAL MAXIMUM ADEQUATE ANTITOXIN LEVEL AND LEVEL TWO YEARS AND LESS THAN TWO YEARS AFTER THE SECOND AND THIRD DOSES OF TOXOID

Twenty-five of the 31 children comprising this series were available for retesting two years after receiving a third, or booster, dose of toxoid. In the table the initial adequate antitoxin titers (when more than one titer was obtained within one month of the administration of toxoid only the maximum titer was recorded) and the titers obtained less than two years (when the titer dropped to the inadequate level) and two years after administration of toxoid are compared. The table also gives data for a comparable group of 51 children who received a third injection of toxoid from three to fifteen months after the second dose and for another group of 129 children who received only two doses of toxoid. The group of 25 children, while admittedly small, nevertheless is impressively adequate, since it shows initial maximum antitoxin titers and titers two years later that are uniformly and significantly higher than the corresponding titers obtained by the other two groups of children.

The table shows that 46 per cent of the 129 children who received two doses of toxoid, 14 per cent of the 51 children who received a third injection from three to fifteen months after the second dose and 4 per cent of the 25 children who received a third injection two years after the second dose of toxoid showed a drop in titer from an adequate maximum initial level to an inadequate level less than two years after receiving the last dose of toxoid.

At the end of two years 72 per cent of the children given the third injection two years after the second dose had 0.1 unit of antitoxin or more per cubic centimeter of serum (group 1). In contrast, only 18 per cent of the children given the third injection from three to fifteen months after the second dose gave as good results (group 2). Nine per cent of the children given only two doses gave comparable results (group 3). The ratios of 4:1 between the first and second groups of children and 8:1 between the first and third groups are largely due to the fact that 100 per cent of the children of the first group, as compared with 70 per cent of the children of the second and with 32 per cent of the children of the third group, had maximum initial titers of from 0.5 to 1 unit or more of antitoxin.

Thus it can be observed that the antitoxin titer of 48 per cent of the 129 children dropped from an adequate to an inadequate level two years or less than two years after the administration of two doses of toxoid and that 10 per cent of the 51 allergic children given the third injection from three to fifteen months after the second dose and only 4 per cent of the 25 children given the third injection two years after the second dose had inadequate titers. Moreover, a higher percentage of the latter 25 children not only attained the highest antitoxin levels after the third dose but two years later 96 per cent of them showed adequate antitoxin levels (up to 0.5 unit of antitoxin per cubic centimeter of serum) as compared with 90 per cent of those given the third injection from three to fifteen months after the second dose and also with 52 per cent of those given two doses who showed adequate levels (up to 0.2 unit of antitoxin).

REACTIONS AND SENSITIVITY

The first 18 of the 31 children comprising the present series were given a third, or "booster," dose of combined alum-precipitated diphtheria and tetanus toxoids. Nine of these 18 children had local reactions of various degrees after the injection of combined toxoids. The reactions were similar to those described in a previous publication.[1] Marked local reactions occurred in 5 children. One child had a slight and 3 children a marked local reaction, and some hours after the injection of the combined toxoids the 4 children experienced an elevation of temperature, ranging up to 104 F., which lasted from one to two days. The incidence of febrile reactions in the group of 18 children is 22 per cent. This contrasts with 3 per cent in the group of 65 children given a third injection of combined toxoids from three to fifteen months after basic immunization and with 1 per cent of those given only basic immunization as reported in previous studies.

The remaining 13 of the 31 allergic children comprising the present series were given a "booster" dose of only alum-precipitated tetanus toxoid. Not 1 of these children showed a febrile or a marked local reaction after the injection of toxoid.

One child of the group of 18 children showed a general allergic reaction after a third injection of combined alum-precipitated diphtheria and tetanus toxoids. The symptoms of the general reaction were an elevation of temperature to 103 F., which lasted for two days, and malaise, vomiting and generalized urticaria, which lasted for one day. Thus far, this was the only allergic systemic reaction encountered in the active immunization of 186 allergic children who have had two to five doses of combined toxoids, including 13 children who have had a third dose of alum-precipitated tetanus toxoid alone, for a total of 471 injections, or an incidence of 0.2 per cent.

The scratch tests performed on the 31 children comprising this study with undiluted combined alum-precipitated diphtheria and tetanus toxoids and alum-precipitated tetanus toxoid did not produce positive reactions, immediate or delayed. The tests were performed prior to and from one to six months (or an average of three and one-half months) after the third, or "booster," dose of toxoid. In view of these negative scratch reactions to the toxoid preparations, the marked local and systemic reactions (elevation of temperature and urticaria) following the "booster" dose of the combined alum-precipitated diphtheria and tetanus toxoids can be attributed to increased sensitivity to diphtheria bacillus protein rather than to the proteose contained in the toxoid preparation. The probability of induced sensitivity to tetanus bacillus protein is remote. In the light of the increased incidence of marked local and systemic reactions following a "booster" dose of combined alum-precipitated diphtheria and tetanus toxoids, it is therefore advisable to employ as a "booster" dose for protection against tetanus alum-precipitated tetanus toxoid only, especially when the "booster" dose is given to older children two or more years after the completion of basic immunization with two doses of the preparation of the combined toxoids.

Local and general reactions following the subcutaneous injection of the combined toxoids were fully discussed in a previous communication.[1]

COMMENT

The importance of the role of allergy in the establishment of immunity was significantly evident throughout this study. When a child has had two injections of combined toxoids a solid foundation for the acceptance of a third, or "booster,"

dose of toxoid is established. The capacity to respond with maximum antitoxin levels to a third injection of toxoid given two years after basic immunization is vividly evidenced by the results obtained with the 31 children comprising this series.

In a previous communication [1] it was observed that the intervals between the two doses of combined toxoids has a direct influence on the antitoxin response. One group of children was given injections of the combined toxoids at intervals of from one to four months and another group at intervals of from five to ten months. A significantly greater percentage of the latter group had responded with the highest antitoxin values. In the present and in the preceding study [2] it was likewise observed that the intervals between the third, or "booster," injection of combined toxoids or alum-precipitated tetanus toxoid alone and the second dose has a direct influence on the antitoxin response. In the preceding study the third and second doses of combined toxoids for 65 children were given at intervals of from five to fifteen months. In the present study the interval between the two doses for 31 children was two years. The vast majority of the latter group have responded with the highest antitoxin values thus far obtained. Whether or not employing a longer interval will result in a further enhancement of the antitoxin response is under investigation.

SUMMARY AND CONCLUSIONS

Two years after the completion of basic immunization with two 0.5 cc. doses of combined alum-precipitated diphtheria and tetanus toxoids, 31 allergic children were given a third, or "booster," dose of 0.5 cc. (18 children received combined alum-precipitated toxoids and 13 children alum-precipitated tetanus toxoid alone). Antitoxin levels were determined at various intervals after the second and after the third dose of the toxoids, and the respective totals of 159 and 194 specimens of blood serum were titrated for tetanus antitoxin.

The incidence of local reactions after the third dose of combined toxoids, after the third dose of tetanus toxoid alone and after the basic immunization was 50, 25 and 25 per cent, respectively. An elevation of temperature which lasted from one to two days occurred only after the third dose of combined toxoids in 22 per cent of the children. This incidence of febrile reactions contrasts with 3 per cent in the group of 65 children given a third injection of combined toxoids from three to fifteen months after basic immunization and with 1 per cent in the group given only the basic immunization.

One systemic allergic reaction (urticaria) was encountered for the first time and occurred in a child given the combined toxoids.

Prior to and from one to six months after the booster dose, negative reactions were obtained to scratch tests with undiluted combined alum-precipitated diphtheria and tetanus toxoids and alum-precipitated tetanus toxoid alone.

The injection of a third, or "booster," dose of combined alum-precipitated diphtheria and tetanus toxoids and alum-precipitated tetanus toxoid alone into allergic children two years after the completion of basic immunization with two doses of combined toxoids was followed within one month in all instances by an adequate tetanus antitoxin titer, which was always higher and lasted for a much longer period than that which followed basic immunization as well as that which followed the third dose of combined toxoids given from three to fifteen months after basic immunization. The antitoxin titer obtained on the seventh day after the third injection of toxoid given two years after basic immunization was always adequate and at its maximum in the majority of instances.

Comparison of the initial antitoxin levels and the corresponding titers one month and two years after administration of the "booster" dose of toxoid for one group of children two years after basic immunization and for another group from three to fifteen months after immunization and for a final group given basic immunization only revealed that the percentage of the first group of children attaining the highest antitoxin levels (0.5 to 1 unit or more of antitoxin) within one month of receiving their last dose was not only significantly higher than of the children of the last two groups (100 as compared with 70 and 32 per cent respectively) but that two years later the ratio between the patients of the three groups who showed an antitoxin titer of 0.1 unit or more was 4:1 (72 and 18 per cent, respectively) for the children of the first and the second groups and 8:1 (72 and 9 per cent, respectively) for the children of the first and the third groups.

Finally, when a child has had basic immunization with two doses of combined alum-precipitated diphtheria and tetanus toxoids and a third, or "booster," injection of toxoid is administered two years later, then alum-precipitated tetanus toxoid alone should be used in order to keep febrile, marked local and systemic reactions at the minimum level.

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CONGENITAL MALFORMATIONS INDUCED IN RATS BY MATERNAL NUTRITIONAL DEFICIENCY

IV. CLEFT PALATE

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Many theories have been advanced concerning the causes of cleft palate. Early theories attempted to explain this developmental defect by abnormal mechanical influences. Abnormal pressure of the mandible and tongue,[1] and interposition of extremities,[2] of tumors [3] or of supernumerary teeth [4] were blamed for the failure of union of the various parts which constitute the normal palate. Amniotic pressure and amniotic bands received special attention as possible causes of facial clefts.[5] Hydrocephalus causing broadening of the base of the skull was also mentioned.[6] None of these theories could be sufficiently supported, and it is thought today that the conditions once considered as causative were only accidental or collateral abnormalities found in the affected persons.

Reports of familial occurrence of cleft lip and palate date back to the eighteenth century,[7] and numerous instances of families in which these malformations occurred repeatedly and through several generations have been observed since. A number of authors have investigated the family background of patients with cleft lip and palate as encountered in hospitals and clinics. The familial occurrence found by the different authors was compiled by Uebermuth.[8] It ranges according to the different estimates between 5.7 per cent [9] and 44.5 per cent.[10] Most investigators

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9. Stobwasser, C.: Die Hasenscharten in der Göttinger chirurgischen Klinik von October 1875 bis Juli 1882, Deutsche Ztschr. f. Chir. **19**:11, 1883.

10. Sanders, J.: Inheritance of Harelip and Cleft Palate, Genetica **15**:433, 1934.

found more than 1 afflicted member in the families of about 20 per cent of their patients. Attempts were made to determine the mode of inheritance of facial clefts from such compilations of family records. However, no consensus was reached. Thus Rischbieth [7] came to the conclusion that cleft lip and palate are not inherited as a unit character but are expressions of "physical degeneracy inherent in certain stocks. . . ." Birkenfeld [11] found a recessive mode of inheritance in 80 per cent of his cases and a dominant mode of inheritance in 20 per cent. Schröder [12] considered the mode of inheritance as recessive in 75 per cent and as dominant in 25 per cent of his cases. He supported the hypothesis of Just,[13] according to which the minor "forms of manifestation" follow the dominant and the severe ones the recessive mode of inheritance. He also supported Just's assumption of action of multiple allelomorphs in the inheritance of cleft lip and palate. According to Sanders [10] there are five hereditary factors for the normal coalescence of the various processes in the facial part of the embryo. If one of these factors is missing, the result is a simple abnormality, while the more complicated clefts are due to the disturbance of several of these genetic factors. Droogleever Fortuyn [14] concluded from the material of the authors previously mentioned that harelip and cleft palate are inherited as a double recessive trait, one gene being autosomal and the other one sex linked. This should explain the fact that harelip is twice as common in the male sex as it is in the female. Mengele [15] included the "microcleft formations" found in members of the families investigated and came to the conclusion that an irregular simple dominant mode of inheritance of the abnormal gene can be recognized, whereby the manifestation depends on other developmental disturbances or other genes.

This lack of agreement indicates that the mode of inheritance of cleft lip and palate in human beings is not well understood at the present time.

Reed and Snell,[16] who found harelip and cleft palate hereditary in a strain of mice, concluded that the malformation behaves genetically "as a recessive subject to normal overlaps." In later publications Reed [17] stated that these malformations result "when a small number of cumulative genes are present in the homozygous condition; provided that chance and environmental conditions are favorable. . . . The other probable hypothesis is that there is one gene which when homozygous allows harelip expression, the extent of which is controlled by many genetic and environmental modifiers." Steiniger [18] also emphasized that environmental factors play an important role in the manifestations of the hereditary tendency to harelip and cleft palate in mice.

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17. Reed, S. C.: Harelip in the House Mouse: (*a*) I. Effects of the External and Internal Environments, Genetics **21**:339, 1936; (*b*) II. Mendelian Units Concerned with Harelip and Application of the Data to the Human Harelip Problem, ibid. **21**:361, 1936.

18. Steiniger, F.: Neue Beobachtungen an der erblichen Hasenscharte der Maus, Ztschr. f. menschl. Vererb.- u. Konstitutionslehre **23**:427, 1939.

The studies on pairs of twins one or both of whom showed facial clefts present a valuable contribution to the etiologic investigation of these deformities. Compilations of the cases reported have been published by Lehmann and Ritter [19] and Schröder.[20] It seems that 15 pairs of identical twins have been reported. In most of these the identity appears well established. Of these identical twins 6 pairs showed cleft formation in both members, while in 9 pairs only one twin had the deformity. Of fourteen pairs of nonidentical twins 1 pair showed corresponding cleft formations and thirteen did not. From the comparison of these identical and nonidentical twins it was concluded that genetic factors play a leading role in the causation of cleft lip and palate.[20] It seems to us, however, that the existence of reports of 9 pairs of identical twins of which 1 member showed a cleft while the other member was normal in regard to this deformity proves that nongenetic factors are also involved in the formation or prevention of harelip and cleft palate.

It seems, therefore, definitely desirable to continue the search for environmental factors which contribute to the manifestation of these malformations.

Maternal malnutrition as an etiologic factor in the formation of oral clefts has been repeatedly suggested. The case of the lionesses of the London Zoo that gave birth to cubs with cleft palates on a certain diet and delivered normal offspring when the diet was changed has been cited repeatedly. However, it seems that experimentation in this case both with food and with water failed to prove any relation between the mother's diet and the occurrence of the defect.[21] A similar report concerns 32 jaguars born of one mother by the same sire in the zoological gardens of Berlin. All the young had cleft palate. At that time the parent animals were fed cold meat from which the blood had been allowed to escape. It is related that when the parent animals were fed with meat which was still warm and which contained blood 25 jaguars were born with normal palates (cited by Brophy [22]). Hale [23] reported the appearance of cleft palate and harelip combined with malformations of the eyes, ears and kidneys in the offspring of 4 sows fed a vitamin A–deficient diet. When this diet was supplemented by cod liver oil or green pasture, normal offspring were obtained. Hale stated that in this instance the evidence against hereditary transmission of the defects was "almost overwhelming," since the deformities had not been observed in the herd previous to the nutritional experiments and the parents of the deformed animals were apparently normal. The 3 sires used for the breeding produced only normal pigs when bred to other sows. When 1 of the deformed males was mated to a normal unrelated gilt or mated back to his dam or mated to his deformed sister and littermate 26 normal and no abnormal pigs were farrowed.

In 1940 we reported congenital malformations in rats induced by maternal nutritional deficiency.[24] About one third of the offspring of mothers reared and bred on a deficient diet (diet 1) appeared anatomically abnormal on external inspec-

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24. Warkany, J., and Nelson, R. C.: Appearance of Skeletal Abnormalities in Offspring of Rats Reared on a Deficient Diet, Science **92**:383, 1940.

tion or after clearing.[25] The abnormalities consisted of shortness of the mandible, shortening or distortion of the extremities, various forms of syndactyly of the hands and feet and fusion of ribs. There was a definite pattern recognizable in these abnormal young, although many degrees of severity of the abnormalities occurred. In 100 cleared abnormal specimens the different skeletal parts were affected with various frequencies indicated in the table.[26]

That these malformations are caused by a deficiency of the maternal diet was shown by the following results:

1. Females of the same strains[27] bred on an adequate stock diet did not produce offspring showing the abnormalities of the "pattern of diet 1."

2. Females of the same strains bred on diet 1 supplemented by 2 per cent dried pig liver also produced normal offspring.

3. When females which had produced abnormal offspring while fed diet 1 were bred again on diet 1 supplemented by liver, the subsequent litters were always free of malformations.

4. When males which had fathered abnormal litters with females fed diet 1 were mated subsequently with females fed the adequate stock diet or the liver-supplemented diet, their offspring were always normal.

*Frequency of Osseous Defects in One Hundred Cleared Abnormal Specimens**

Tibia	93	Ulna	50
Mandible	80	Humerus	34
Ribs	75	Hind foot	31
Fibula	63	Scapula	6
Radius	58	Clavicle	6
Hand	54	Femur	1
Sternum	52		

* Since only one third of the offspring obtained on diet 1 were abnormal, the frequency of the various defects in the total offspring born of mothers fed diet 1 is about one third of the values recorded in the table.

Further studies of the offspring of mothers reared and bred on diet 1 revealed that cleft palate was also a part of the pattern of diet 1. The palates of 300 young born of mothers fed this deficient diet were examined by oral inspection, and cleft palate was found in 44 young, i. e. in 14.7 per cent. The 300 offspring were a fairly representative sample of the 1,500 young obtained on this diet up to the present time. They consisted of 200 specimens which appeared externally normal and 100 specimens which were deformed. For comparison with the percentage figures listed in the table, it may be stated here that cleft palate occurred in 44 per cent of the abnormal specimens. Thus cleft palate is a frequent abnormality in the pattern of diet 1, but it occurs less often than the deformities of the tibia, mandible, ribs and other parts (see the table).

The cleft of the palate is V-shaped, being narrower in front and wider in its posterior part (fig. 1 *B*). It extends anteriorly to the incisive papilla and does not

25. Warkany, J., and Nelson, R. C.: Skeletal Abnormalities in Offspring of Rats Reared on Deficient Diets, Anat. Rec. **79**:83, 1941.

26. Warkany, J., and Nelson, R. C.: Skeletal Abnormalities Induced in Rats by Maternal Nutritional Deficiency: Histological Studies, Arch. Path. **34**:375 (Aug.) 1942.

27. The Sprague-Dawley strain (Madison, Wis.) and a strain from Baltimore were used with essentially the same results. (Warkany, J.; Nelson, R. C., and Schraffenberger, E.: Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency: II. Use of Varied Diets and of Different Strains of Rats, Am. J. Dis. Child. **64**:860 [Nov.] 1942).

affect the alveolar processes or the lips. The cleft is due to a lack of fusion of the palatine processes of the maxillas and the horizontal processes of the palatine bones. Such an anatomic deformity causes a wide communication between the oral and nasal cavities in man. In the rat, however, the results are different because of the anatomic structure of the nose. The nose of the rat consists of an anterior nasal space, which contains the maxilloturbinal, a superior space, the ethmoid region and the posterior part, the nasopharyngeal duct. This duct connects the anterior and superior spaces with the pharynx. It communicates with the anterior and upper parts of the nose through two oval openings, the choanae. Behind these openings the nasopharyngeal duct is separated from the ethmoid region by a horizontal plate, which is cartilaginous in the newborn animal. Thus, in the case of cleft palate a communication exists between the nasal and oral cavi-

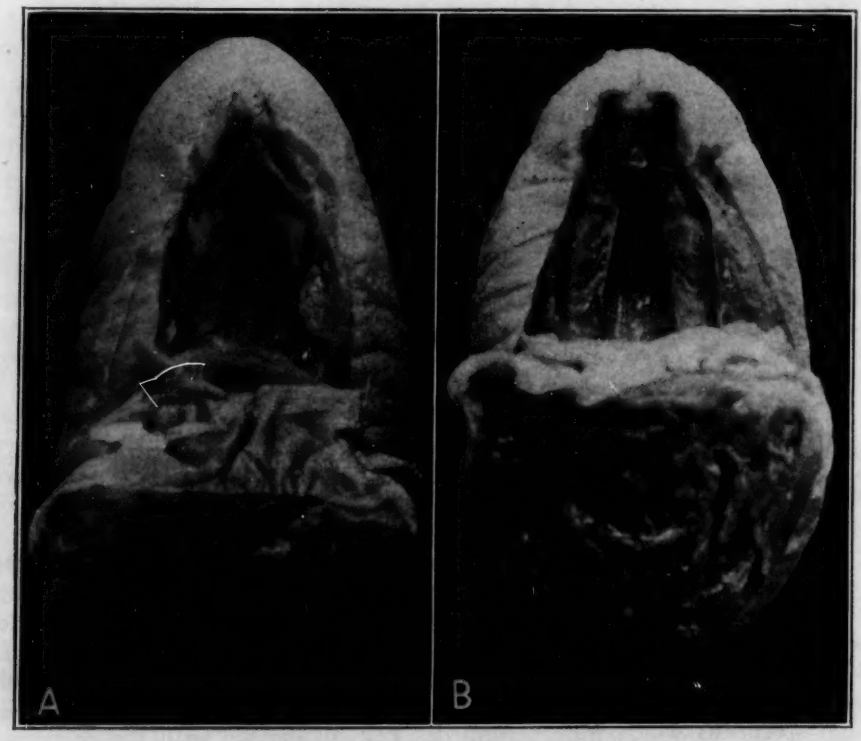

Fig. 1.—*A*, normal palate of newborn rat. *B*, cleft palate.

ties through the choanae only (fig. 2), while the nasopharyngeal duct communicates with the oral cavity throughout its length.

In a number of abnormal specimens in which the tongue and mandible were removed, a partial cleft was found, limited to the posterior part of the palate (fig. 3). This type of cleft palate cannot be seen on simple oral inspection and was not included in the percentage figures given in the table. We have the impression also that in many abnormal specimens the palates were high and arched though not cleft.

The typical form of cleft palate observed in the pattern of diet 1 (fig. 1 *B*) closely resembles the physiologic cleft palate seen in rat fetuses (fig. 4). It represents obviously the product of arrested development, the continuation of a fetal condition into postnatal life.

This type of cleft palate has been observed in other mammals [28] as well as in man. It corresponds to group II of Ritchie's classification [29] of congenital clefts (post-alveolar-process cleft). Estimates of the incidence of this type of cleft palate in human beings vary a great deal. Sanders [10] found "uncomplicated cases of cleft palate" in 8.7 per cent of his cases of facial clefts; Ritchie,[29] in 12.8 per cent; Birkenfeld,[11] in 16.6 per cent; Schröder,[30] in 26.6 per cent, and Burdick,[31] in 27.2 per cent. Post-alveolar-process clefts are apparently rare in the strains of mice in which hereditary clefts have been observed. In these animals the combination of harelip and alveolar clefts is the rule, while the type of cleft palate seen in our experiments is the exception.

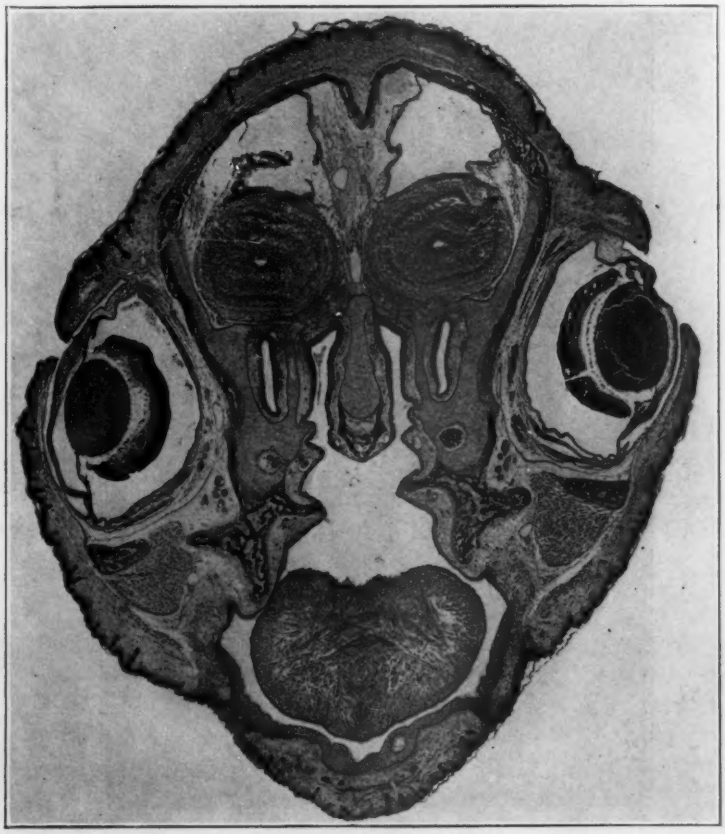

Fig. 2.—Transverse section of head of abnormal newborn rat with cleft palate, showing communication between nasal and oral cavities.

Of 44 specimens with cleft palate examined by us, 12 were male, 28 were female and for 4 the sex could not be determined. Reed [17a] found more male

28. Keith, A.: Three Demonstrations on Congenital Malformations of Palate, Face, and Neck, Brit. M. J. **2**:363, 1909. Rischbieth.[7] Uebermuth.[8]

29. Ritchie, H. P.: Congenital Clefts of the Face and Jaws, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Co., 1942, vol. 5, chap. 9.

30. Schröder, C. H.: Untersuchungen über die Vererbung der Hasenscharte und Gaumenspalte mit besonderer Berücksichtigung des Erbgangs, Arch. f. klin. Chir. **182**:299, 1935.

31. Burdick, C. G.: Hare-Lip and Cleft Palate: Analysis of One Hundred and Eighty-Four Cases, Ann. Surg. **92**:35 and 136, 1930.

than female mice in his strain affected with hereditary harelip and cleft palate. In human beings harelip and cleft palate are also preponderant in males.[32] However, in regard to post-alveolar-process clefts this predominance among males apparently does not exist.[33]

In our experience the malformations of the pattern of diet 1 are rarer in first litters than in subsequent litters. We explained this fact by assuming that a store of the protective factor present in the mother at the beginning of the breeding experiment becomes exhausted during one or more pregnancies.[34] In mice with hereditary clefts, however, Steiniger [18] found a higher incidence of the deformities in the members of earlier litters than in those of later litters. Reed [17a] observed

Fig. 3.—Partial (posterior) cleft palate.

of mice that younger mothers had relatively more offspring with hereditary clefts than older mothers. Thus in regard to incidence of cleft formation with progressing litter number one finds a behavior in mice with hereditary clefts different from that in rats with clefts due to maternal nutritional deficiency.

Every specimen with cleft palate showed one or several associated malformations. These were found to conform entirely with those of the pattern of diet 1 and need not be described here again. Of special interest was the micrognathia

32. Sanders,[10] Ritchie,[29] Schröder [30] and others.

33. Sanders.[10] Ritchie.[29]

34. Warkany, J., and Nelson, R. C.: Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency, J. Nutrition **23**:321, 1942.

which was seen in all but 1 specimen with cleft palate. The shortness of the mandible was due to reduction of the corpus mandibulae only, while the ramus was never severely affected (fig. 5 *B*). The unerupted incisors, which can be seen in the normal cleared specimen and in the specimens with milder forms of micrognathia, were absent in the animals with extreme deformities. The tongues of the abnormal animals were well developed and protruded when there was micrognathia.

Fig. 4.—Physiologic cleft palate in a rat fetus.

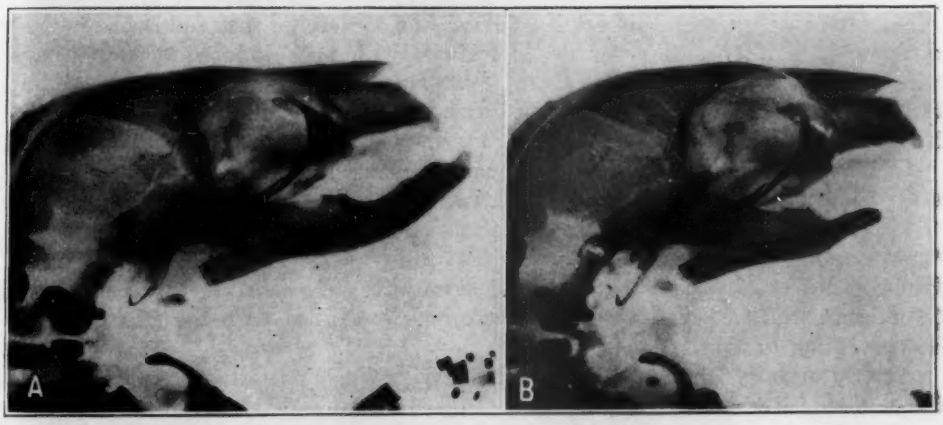

Fig. 5.—*A*, cleared head of normal newborn rat. *B*, cleared head of abnormal newborn rat, showing micrognathia.

Litter mates of the young rats with cleft palates were occasionally free from this anomaly, but more often they also had cleft palates, and several young with clefts were derived from different litters of the same mother fed diet 1. Thus a "familial" incidence of cleft palate was frequently observed in the pattern of diet 1.

Offspring of mothers of the same strains who were fed different diets were employed as controls. The palates of 250 young which were born of females reared and bred on an adequate stock diet [34] were examined by oral inspection. In no instance was there cleft palate. In addition, the palates of 100 young which were born of mothers reared and bred on diet 1 supplemented by 2 per cent dried pig liver were inspected in the same way. None of these young showed a cleft palate.

It appears, therefore, that a nutritional factor deficient in the maternal diet 1 but present in large amounts in liver is a factor in the causation and prevention of cleft palate in the newborn rats described in this study.

COMMENT

The occurrence of cleft palate as a constituent of a syndrome of congenital malformations produced by a deficient maternal diet proves that this deformity may be due to unfavorable environmental conditions. It seems that the lack of a certain nutritional factor necessary for the normal fetal development of the rat interferes in some way with the orderly progress of differentiation and leads thus to the malformations described as the pattern of diet 1. Thus cleft palate appears in this pattern as a nonhereditary modification.

On the other hand, we have learned from the observations of Cloudman,[35] Reed and Snell [16] and Steiniger [18] that harelip and cleft palate have appeared as a genic mutation in a certain strain of mice. These investigators have observed various degrees of expression of harelip and cleft palate not seen by us. However, certain forms of cleft palate due to genic influences appearing in these mice are anatomically identical with the cleft palates produced in rats by maternal nutritional deficiency. This is best illustrated by a comparison of figure 6 *a* in Steiniger's [18] article with figure 1 *B* in this report. They both represent post-alveolar-process clefts, one caused by a mutated gene and the other caused by environmental interference.

Several abnormalities are known which can be due to either mutation or environmental modification.[36] "This duplication of the effects of a mutation by an environmental modification is of such frequent occurrence that Goldschmidt has coined a special term to designate individuals with such induced defects—they are phenocopies. It may be assumed that environmental agencies alter some developmental processes in the same way that gene changes or other mutations do." [37]

Cleft palate due to maternal nutritional deficiency represents another example of a phenocopy which simulates a hereditary defect.

It remains to be seen whether the lack of a nutritional factor plays a role in the causation of cleft palate in man. Nevertheless the theoretic possibility of phenocopies of cleft palates suffices to demonstrate some fallacies which underlie the interpretations in certain recent publications concerned with the etiology and the prevention of this anomaly.

Several authors who studied the inheritance of these malformations in human beings assumed that all their patients had hereditary cleft formations. They considered this assumption justified because attempts to explain harelip and cleft

35. Cloudman, A. M.: Genetic Studies in Hare-Lip, Proc. Internat. Cong. Genet. **2**:26, 1932.

36. Landauer, W.: Untersuchungen über Chondrodystrophie; allgemeine Erscheinungen und Skelett chondrodystrophischer Hühnerembryonen, Arch. f. Entwcklngsmechn. d. Organ. **110**: 195, 1927. Danforth, C. H.: Artificial and Hereditary Suppression of Sacral Vertebrae in the Fowl, Proc. Soc. Exper. Biol. & Med. **30**:143, 1932. Goldschmidt, R. B.: Physiological Genetics, New York, McGraw-Hill Book Company, 1938.

37. Dunn, L. C.: Heredity and Development of Early Abnormalities in Vertebrates, in Harvey Lectures, 1939-1940, Lancaster, Pa., Science Press Printing Company, 1940, p. 135.

palate by mechanical and other environmental influences had failed. One author expressed the opinion that previous investigations have made it clear that the heredity of cleft formation is beyond doubt and that other, exogenous, causes are of no importance.[6]

The acceptance of this opinion may lead to extremely radical suggestions. Haentzschel[38] claimed that all cleft formations must be regarded as hereditary. Although he found familial occurrence in only 20 per cent of his patients, this author considered the remaining 80 per cent also of hereditary origin, since no other explanation of these anomalies had been advanced. He concluded that all patients with cleft palate should be sterilized.

It is to be hoped that the production of cleft palate in laboratory animals by maternal nutritional deficiency will somewhat moderate the eugenic zeal of such authors or direct it into rational channels.

Other students of cleft palate in man[39] have recognized the fallacies which led to the erroneous conclusions cited. They have pointed out, correctly, that on the basis of present day knowledge of the occurrence of clefts in sibships, families, twins and individuals one can conclude that environmental factors play an important role in the manifestations of these deformities. The investigators who studied hereditary harelip and cleft palate in mice also found nongenetic factors to be influential in the expression of the hereditary tendency. Reed[17a] summarized as follows: "In mice there are differences in harelip expression resulting from the action of both environmental and genetic factors. Differences in harelip expression depend upon the sex of the individual, the size of the litter in which the individual was born, the age of its mother, asymmetry of the clefts, and in large part upon intangible chance factors . . ." Steiniger,[18] after studying the various manifestations of the underlying hereditary tendency in mice, considered it possible that they may be influenced by the administration of growth-promoting or growth-inhibiting factors. He stated that it is conceivable that endocrine or nutritional factors may modify the hereditary tendency.

The experiments reported in this communication should encourage attempts to modify facial cleft formations in strains, and also in families, in which such malformations are hereditary. Whether modification by nutritional measures will be possible or not, the experimental production of phenocopies of cleft palates proves that it is not justifiable to assume a priori that all cleft palates in human beings are hereditary, an assumption which underlies many recent studies on this subject. It is more likely that the clinical material encountered is a conglomeration of hereditary malformations and phenocopies. It is obvious that a study of the mode of inheritance of this malformation requires the exclusion of all phenocopies from the study. Otherwise, an entirely faulty picture is obtained in such studies of heredity by inclusion of genotypically normal families in which a phenocopy has appeared.

The appreciation of this point leads to the question of whether it is possible to distinguish clinically between hereditary cleft palate and a phenocopy. This question is of the utmost importance, for planners of eugenic measures and several authors have ventured to establish rules for the distinction of hereditary from nonhereditary cleft palates and other malformations.

Investigation of the family history is usually considered the best method for the establishment of heredity of an abnormal trait, whereby its repeated occurrence in a family or sibship is often accepted as proof of heredity.

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38. Haentzschel, K.: Die eugenische Bedeutung der angeborenen Spaltbildungen im Bereiche von Lippe, Kiefer and Gauman, Dissert., Leipzig, A. Edelmann, 1935.

39. Axhausen, G., cited by Steiniger.[18] Lehmann and Ritter.[19]

Such reasoning is open to question, since a high familial incidence of deformities does not necessarily indicate that they are genetically determined. It may be remembered that Siegert [40] in 1903 declared on the basis of careful family studies that "heredity is one of the most important etiologic factors in rickets," an opinion which will not find many supporters today. It is obvious that unfavorable environmental conditions can affect whole families, and thus their effects will imitate those of hereditary transmission. Endemic cretinism often affects several members of a family, but it is, nevertheless, caused by environmental influences, probably lack of iodine in the food of the mother. Hale's [23] experiments as well as ours illustrate that unfavorable prenatal nutrition can cause familial, though not hereditary, congenital malformations.

On the other hand, it has been pointed out, correctly, that the occurrence of a pathologic trait or a malformation in only 1 member of a human family does not exclude the possibility of its genetic determination. This can be explained on several bases; smallness of human families; difficulties in obtaining correct histories, particularly in respect to miscarriages and deaths in early infancy; skipping of one or more generations; appearance of microforms or vicarious malformations; dependence of the trait on the combination of multiple factors, and others.

Thus family records per se, whether "positive" or "negative," neither prove nor exclude genetic determination.

The frequent association of cleft lip and palate with other congenital malformations has been mentioned by many authors [41] and often accepted as proof of their heredity. This concept dates back to an investigation by Haymann,[42] who found in 1903 that some of these associated defects could not be explained by amniotic anomalies and concluded that such multiple deformities must therefore be due to internal causes, particularly to heredity. Recent authors [43] also considered multiple malformations which affect a whole anatomic system as genetically determined, and Lenz [44] declared: "When malformations are symmetrical, there can be little doubt that they are truly hereditary. If for instance, we find the same malformation in both hands, we can conclude with the greatest probability that the trouble is hereditary. The same thing applies to malformations which exhibit a serial homology, being of the same character both in the hands and in the feet."

The production by maternal nutritional deficiency of cleft palate frequently accompanied by systemic and symmetric defects of the hands and feet disproves the foregoing citations. The association of cleft palate with other, systemic, symmetric and serial, malformations does not indicate that it is hereditary.

Although the coexistence of cleft palate with other congenital malformations does not prove genetic determination, it would be conceivable that certain associated defects are more frequent with the hereditary anomaly while others are more common with cleft palate of environmental origin. The fact that harelip was never observed in the pattern of diet 1 while it is the rule in the hereditary pattern of mice seems to support such an assumption. Since, however, isolated postalveolar-process clefts, without harelip and alveolar clefts, occur also in the hereditary pattern, a certain overlapping of the two syndromes exists. There is also

40. Siegert, F.: Beiträge zur Lehre von der Rachitis, Jahrb. f. Kinderh. **58**:929, 1903.

41. Schröder, C. H.: Erbliche Beziehungen der Hasenscharte und Gaumenspalte zu anderen körperlichen Missbildungen, Beitr. z. klin. Chir. **169**:402, 1939. Rischbieth.[7] Sanders.[10] Birkenfeld.[11] Mengele.[15]

42. Haymann, T.: Amniogene und erbliche Hasenscharten, Arch. f. klin. Chir. **70**:1033, 1903.

43. von Verschuer, O.: Woran erkennt man die Erblichkeit körperlicher Missbildungen? Arch. f. klin. Chir. **193**:185, 1938.

44. Baur, E.; Fischer, E., and Lenz, F.: Human Heredity, New York, The Macmillan Company, 1931.

overlapping of at least one associated defect in these two patterns. Defects of the eyes in mice with hereditary harelip were mentioned by Reed and Snell [16] and Steiniger.[18] In a small number of the rats with malformations of the pattern of diet 1, "open eye" at birth, the defect recorded by Steiniger, has also been observed by us.

In human beings almost every type of malformation has been described associated with cleft palate. Syndactyly, splithand, brachydactyly, defects of the radius, clubfoot and defects of the eye are some of the more frequent ones; they are also seen in the rats with defects of the pattern of diet 1. On the other hand, neither polydactyly nor defects of the spinal column have been seen in the syndrome produced in rats by maternal nutritional deficiency.

Micrognathia, a regular companion of cleft palate in the pattern of diet 1, is rarely mentioned as an associated malformation in the literature on harelip and cleft palate. However, the combination of micrognathia and cleft palate does occur in children and seems to represent a well defined syndrome. Infants with these defects suffer from attacks of cyanosis due to displacement of the tongue toward the pharynx. Thirteen cases of this syndrome have been described in the literature.[45] It is of interest to note that the 13 infants with this syndrome had post-alveolar-process clefts (group II of Ritchie) and none of them had a harelip. The micrognathia in these cases was apparently due to hypoplasia of the corpus mandibulae, while the ramus was little affected.[45c] The types of micrognathia and cleft palate described in these cases resemble those of the pattern of diet 1. However, the tongue, which is large and protruding in the pattern of diet 1, was small in the children described.

The combination of micrognathia and post-alveolar-process cleft is probably more prevalent in children than is indicated by the small number of cases cited here. In fact, the concurrence of these two deformities has been used by Tandler [1b] as an argument for the role of the tongue in the causation of cleft palate. Ritchie [29] also emphasized that in association with post-alveolar-process cleft an underdevelopment of the mandibular process is so frequently found that it is easy to conceive that the base of the tongue is pushed up between the two halves of the soft palate and thus interposition of tissue must be considered as a cause of the cleft formation. Lenstrup,[45c] however, stated that it is "most probable that the cleft palate is a consequence of the same developmental inhibition that produces hypoplasia of the lower jaw and that its presence is a co-ordinate phenomenon without any independent significance." It seems of interest that familial occurrence has not been recorded in these cases of micrognathia combined with cleft palate.

It would be too early to identify this clinical picture with the pattern of diet 1 or to state that it may have a similar origin as the deformities described in our experiments.

At the present time it may suffice to restate the fact that cleft palate and associated malformations can be produced by maternal nutritional deficiency. Further

45. (*a*) Lannelongue, O.-M., and Ménard, V.: Affections congénitales, Paris, Asselin & Houzeau, 1891, pt. 1, p. 266. (*b*) Shukowsky, W. P.: Zur Ätiologie des Stridor inspiratorius congenitus, Jahrb. f. Kinderh. **73**:459, 1911. (*c*) Lenstrup, E.: Hypoplasia Mandibulae as Cause of Choking Fits in Infants, Acta pædiat. **5**:154, 1925. (*d*) Eley, R. C., and Farber, S.: Hypoplasia of the Mandible (Micrognathy), Am. J. Dis. Child. **39**:1167 (June) 1930. (*e*) Davis, A. D., and Dunn, R.: Micrognathia: A Suggested Treatment for Correction in Early Infancy, ibid. **45**:799 (April) 1933. (*f*) Callister, A. C.: Hypoplasia of the Mandible (Micrognathy) with Cleft Palate, ibid. **53**:1057 (April) 1937.

observations on human beings and additional experimentation on animals will show whether a distinction between mutations and modifications can be made in clinical cases.

CONCLUSIONS

Attempts to establish the mode of inheritance of harelip and cleft palate based on the assumption that all such deformities in human beings can be explained by genetic factors only have not resulted in congruous results.

Studies of these malformations in human twins and in strains of mice with a hereditary tendency to harelip and cleft palate have led to the conclusion that nongenetic factors modify the manifestations of the pathologic tendency to a great extent.

Harelip (studied by Hale) and cleft palate have been produced by maternal nutritional deficiency in strains of animals which were free of these malformations under adequate nutritional conditions.

It seems that the normal processes of fetal development which lead to the formation of the normal palate can be disturbed by environmental modification as well as by genic mutation.

It is probable that in human beings also cleft palate can be due to modification as well as to mutation.

There seems to be no reliable method available at the present time to ascertain in a given case whether the anomaly is due to genetic or to environmental disturbance.

Eugenic measures for the prevention of harelip and cleft palate must consider environmental as well as genetic factors.

Children's Hospital.

ATTEMPTS TO ENHANCE VIRULENCE OF HAEMOPHILUS PERTUSSIS BY SERIAL PASSAGE IN MICE

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In 1940 Strean [1] described the use of pertussis endotoxin as a cutaneous test to determine susceptibility to pertussis. In subsequent publications the same author [2] described the preparation and properties of pertussis endotoxin and clinical studies in immunity to pertussis with the use of pertussis-skin-testing toxin and antiendotoxin. This work has been confirmed, in the main, in recent publications by Lapointe [3] and Evans.[4]

Since the potency of the toxin produced by Haemophilus pertussis phase I seems to parallel the virulence of the organism,[5] an attempt was made to enhance the virulence by serial passage in mice.

In these experiments six strains of H. pertussis phase I were used, ranging in age from 6 months to 6 years and cultivated on modified Bordet-Gengou medium for approximately forty to five hundred generations. The organisms grown on modified Bordet-Gengou medium responded to all the tests for a smooth phase I organism throughout the long periods of maintenance on this medium.

The minimum lethal dose was determined for each strain on the basis of the least number of living organisms found necessary consistently to kill white mice weighing 18 to 22 Gm. in seventy-two hours. For these strains it ranged from 2,500,000,000 organisms to 20,000,000,000 suspended in 1 cc. of physiologic solution of sodium chloride. The minimum lethal dose was established for each of the strains by repeated trials, and this dose of living organisms was given intraperitoneally to mice as a series of passages alternating with culture on modified Bordet-Gengou medium. When an animal died its peritoneal contents were cultured on a modified Bordet-Gengou plate and the harvest suspended in the same volume of saline solution as in the original suspension and 1 cc. injected intraperitoneally into another animal. If the second animal died, its peritoneal contents were likewise cultured and resuspended in a saline solution and 1 cc. injected intraperitoneally into a third animal. This procedure was continued for four series.

RESULTS

All of the mice died after the first injection of the minimal lethal dose of the organisms. The exudates recovered from the peritoneal cavities of the dead mice

From the Research and Biological Laboratories, Ayerst, McKenna & Harrison, Ltd.

1. Strean, L. P.: A Skin Test for Susceptibility to Pertussis, Canad. M. A. J. **42**:525 (June) 1940.

2. Strean, L. P., and Grant, G. A.: The Preparation and Properties of Haemophilus Pertussis Endotoxin, Canad. M. A. J. **43**:528 (Dec.) 1940. Strean, L. P.; Lapointe, D., and Dechene, E.: Clinical Studies in Immunity to Pertussis with the Use of Pertussis Skin Testing Toxin and Antiendotoxin, ibid. **45**:326 (Oct.) 1941.

3. Lapointe, D., and Strean, L. P.: Etude sur la sérothérapie de la coqueluche, Laval méd. **7**:265 (May) 1942.

4. Evans, D. G.: Antigenic Properties of Haemophilus Pertussis in Relation to Active Immunization, Lancet **1**:529 (May 2) 1942.

5. Strean, L. P.: Active and Passive Immunization with Haemophilus Pertussis, Thesis, Faculty of Graduate Studies and Research, McGill University, 1942.

failed in some instances to kill mice inoculated with this material. When this happened, it was assumed that insufficient numbers of organisms were present in the exudate to equal one minimum lethal dose. For this reason the organisms were cultured from the exudate on modified Bordet-Gengou medium and resuspended in the same volume of saline solution as the original suspension for that strain. It was observed that the number of organisms decreased with increasing passages through mice and recultivation on modified Bordet-Gengou medium. The Petri dishes containing the medium were standard in size, and the spreading was done uniformly. Since the original minimum lethal dose was determined from one plate and the culture was suspended in a calculated volume of saline solution, the succeeding resuspensions were made in a similar volume of saline solution. All standardizations and calculations were made with the aid of the Evelyn photoelectric colorimeter.

The characteristic pathologic picture seen in mice dying after intraperitoneal injections of phase I H. pertussis organisms is a hemorrhagic exudative type, particularly in the peritoneal wall. This appearance was most typical in those animals which died after the injection of the first recovered exudate before recultivation of the organisms. This effect presumably was due to the fact that many of the

Attempts to Enhance Virulence of Haemophilus Pertussis by Serial Passage in Mice *

Strain	No. of Bacilli per Minimal Lethal Dose in 1 Cc., Millions	Generation	First Series: Number Inoculated	First Series: Fate of Animal in 72 Hr. D	First Series: Fate of Animal in 72 Hr. S	First Series: Pathologic Reaction	Second Series: Number Inoculated	Second Series: Fate of Animal in 72 Hr. D	Second Series: Fate of Animal in 72 Hr. S	Second Series: Pathologic Reaction	Third Series: Number Inoculated	Third Series: Fate of Animal in 72 Hr. D	Third Series: Fate of Animal in 72 Hr. S	Third Series: Pathologic Reaction	Fourth Series: Number Inoculated	Fourth Series: Fate of Animal in 72 Hr. D	Fourth Series: Fate of Animal in 72 Hr. S	No. of Passages Resulting in Death
595	2,500	350	3	3	0	++	3	3	0	+++	3	2	1	++	3	0	3	3
18	5,000	40	3	3	0	++	3	3	0	+++	3	1	2	++	3	0	3	2+
138	5,000	400	3	3	0	++	3	3	0	+++	3	1	2	++	3	0	3	2+
Mont	10,000	500	3	3	0	++	3	3	0	+++	3	0	3	....	..	..	..	2
Lind	10,000	150	3	3	0	++	3	3	0	+++	3	0	3	....	..	..	..	2
4246	20,000	300	3	3	0	++	3	1	2	+?	3	0	3	....	..	..	..	1+

* Explanation of symbols: D, dead; S, survived; +++, pronounced reaction; ++, moderate reaction; +, mild reaction.

organisms had autolyzed and liberated their endotoxin. In order to prove this point, the exudate from those animals possessing a copious amount was centrifuged and the supernatant liquid reinoculated into another series of mice. These mice died with typical pathologic lesions and in some instances when less than 1 cc. of this bacteria-free material was injected. The results of these experiments are outlined in the table.

COMMENT

The results observed in these experiments seem to suggest that phase I H. pertussis organisms do not multiply in the peritoneal cavity of the mouse by the procedure described. However, if the organisms recovered from the exudate were recultured on modified Bordet-Gengou medium, resuspended in saline solution and standardized to contain a similar number of organisms per cubic centimeter as were present in the original inoculation of the first series, no loss in virulence was found. As a matter of fact, repeated trials showed that the original virulence was maintained in this manner.

Toomey and Takacs [6] attempted to enhance the virulence of H. pertussis by serial passage in guinea pigs and concluded that the virulence is reduced in the

6. Toomey, J. A., and Takacs, W. S.: Attempts to Enhance Virulence of Haemophilus Pertussis by Serial Passage in Guinea Pigs, Am. J. Dis. Child. **59**:94 (Jan.) 1940.

peritoneal cavity of these animals. In their experiments they carried the exudate from pig to pig and finally found that the exudate failed to kill guinea pigs. It would appear that they did not take into consideration the possibility that the organisms' autolyzing in the peritoneal exudate and thereby liberating their endotoxin accounted for the death of their animals. It is probable that in the serial passages the number of organisms contained in the peritoneal exudate was reduced and so less and less toxin was liberated until ultimately an exudate was found which was so small in volume and in amount of endotoxin and so depleted in number of organisms that their animals survived.

Judging by the experiments reported now, had Toomey and Takacs cultured the exudate and worked quantitatively they would have detected a reduction in number of organisms with each passage and might have arrived at different conclusions.

CONCLUSIONS

While these experiments on mice confirm the conclusion of Toomey and Takacs that H. pertussis does not multiply in the peritoneal cavity of the experimental animals used, they do not, however, confirm the conclusion that virulence is reduced by animal passage; on the contrary, the results suggest that virulence is maintained.

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ELECTROENCEPHALOGRAPHY ON CHILDREN

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MILWAUKEE

INTRODUCTION AND DEFINITION

Electroencephalography is one of the new diagnostic methods in medical science in general and in neurology in particular. It has proved to be an aid in understanding convulsive disorders [1] and in localizing organic disturbances of the brain.[2] While a few years ago the establishing of idiopathic epilepsy as a diagnosis was also the final word in its understanding, electroencephalography has opened new ways for approaching this interesting subject. Electroencephalograms are still in their early stage of development, and too much enthusiasm about their accomplishments is not warranted. But if not only the indications and possibilities [3] but the limitations and technical insufficiencies are kept in mind, electroencephalography will teach physicians much and will direct them to a better view of cerebral physiology and pathology.

The word electroencephalography refers to recording of the electric activity of the brain from the cortex itself, from the periosteum or from the unopened skull. Although all three means have been tried successfully, only electroencephalograms from the surface of the scalp have been used at the Milwaukee Children's Hospital.

HISTORY

Several European investigators observed between 1874 and 1924 that an electrical activity of the cortex of the brain in dogs and rabbits exists and can be recorded with galvanometers directly from the brain or even through the unopened skull. Berger, in Jena, was the first person who recorded electrical activity from the human brain. He demonstrated that the brain has a rhythmic electrical beat produced by the normal function of groups of neurons independent of the vascular and respiratory rhythms. The rhythmic beat as demonstrated by Berger and all later investigators manifests itself as a composition of sinusoidal waves of various heights, frequencies and shapes.

TECHNIC

The electrodes used are small metal plates, about 5 mm. in diameter; fine insulated wires lead from the electrodes to the electroencephalograph. Any type of electrocardiograph jelly can be used between the electrodes and the scalp to improve conduction; the small plates are held in place with flexible collodion that is allowed to dry. The number and placement of electrodes vary from one clinic to another

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From the Milwaukee Children's Hospital.

1. Byers, R. K.: Electroencephalography, J. Pediat. **18**:811 (June) 1941. Gibbs, F. A.: Electroencephalography in Epilepsy, ibid. **15**:749 (Dec.) 1939. Logan, G. B.: Electroencephalography, Staff Meet. Bull. Hosp. Univ. Minn. **11**:412 (May) 1940.

2. (*a*) Gibbs, F. A., and Gibbs, E. L.: An Atlas of Electroencephalography, Boston, The Authors, 1941. (*b*) Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941. (*c*) Yeager, C. L.; Baldes, E. J.; Craig, W. McK., and Woltmann, H. W.: Electroencephalography as Aid in Localizing Intracranial Lesions, Proc. Staff Meet., Mayo Clin. **15**:147 (March 6) 1940.

3. Lennox, W. G.: Gains Against Epilepsy, J. A. M. A. **120**:449 (Oct. 10) 1942.

and depend also on the particular subject. In most instances I have used six active and two inactive electrodes. This enables us to take monopolar and bipolar leads. A bipolar lead is produced by connecting two scalp electrodes with each other; a monopolar lead is obtained by comparing one active scalp electrode with a zero point, e. g. an electrode fastened to the inactive ear lobe. While bipolar leads indicate the difference between the activities of two active areas of the brain, the latter method shows the absolute potential. While for localizing purposes the bipolar leads are preferable, in idiopathic epilepsy the monopolar method of examination will give the more information.

The normal voltage from the unopened skull varies from 10 to 100 microvolts, a microvolt being a millionth of a volt. The voltage is best amplified to a well recordable degree by a series of cathode tubes. The waves are recorded by ink-writers through three independent channels; they are measured and judged according to their frequency, voltage and pattern. To keep out external electrical interference, the patient is placed in a copper-screened room or part of a room under so-called "standard conditions." That means that the patient should lie down perfectly relaxed, should not concentrate and should keep his eyes closed; the room should be quiet and not too light. Any anxiety, excitement, noise, moving of the eyes or movement of the jaws will interfere with good tracings to a greater or less degree.

NORMAL ELECTROENCEPHALOGRAMS

The size and shape of the electroencephalographic waves vary from one person to the other. The variations in brain waves have frequently been compared to variations in handwriting [4]: One hundred persons may write the same few words, but each record will be different from all the others. Extensive studies and comparisons have been made between the electroencephalograms of identical twins and other relatives. It will suffice to mention that the heredity of cerebral dysrhythmias is an established fact and that the science of genetics will have to take into account these electroencephalographic dysrhythmias and not just the clinical manifestations of patients who have epileptic fits.[5] Between 5 and 10 per cent of all clinically normal persons have abnormal tracings; a large proportion percentage of these are relatives of persons known to have epilepsy. These persons are usually called epileptoid or potentially epileptic, and their brain waves are designated as epileptic equivalents. They transmit their dysrhythmias and are exceedingly prone to have clinically epileptic children if they marry epileptoid spouses.

The normal frequency in adults and in older children varies between 8 and 12 waves per second; the regular rhythm in this frequency is called the alpha rhythm; at least 90 per cent of all waves in a normal record should be alpha waves; they are best seen in the occipital area. The voltage may vary anywhere from 10 to 60 or even up to 100 microvolts with small periodic changes in form of spindles. Sudden, sharp changes in a well relaxed patient are abnormal. Other normal rhythms are the so-called beta and gamma rhythms, characterized by frequencies of 15 to 30 and 35 to 60 respectively. Their meaning and importance in the normal electroencephalogram are but little understood. All activity below the frequency of 8 per second is called delta activity. Delta waves occurring in more than 5 to 10 per cent of the record are definitely abnormal in adults and in children above the age of 10 years. The younger the child is, the slower are the waves; and tracings that should be considered abnormal for an adult will frequently be called within normal

4. Davis, H.: Electroencephalography, J. A. M. A. **117**:983 (Sept. 20) 1941.

5. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: Inheritance of Cerebral Dysrhythmia and Epilepsy, Arch. Neurol. & Psychiat. **44**:1155 (Dec.) 1940.

limits for a young child. The newborn child has few, slow and low brain waves without regular rhythm; they appear first in the parietal areas and next in the occiput, when vision becomes more mature.[2a]

ABNORMAL ELECTROENCEPHALOGRAMS

Differentiation between normal and abnormal electrograms is made according to frequency, amplitude, form, pattern and localization of waves. The three main qualities to be looked for are bradyrhythmia (delta activity), tachyrhythmia (high frequency) and hypersynchrony (i. e. abnormal high voltage).

Bradyrhythmia is usually found in sleep, at the border of a cerebral neoplasm, in cerebral edema, in stupor, in hyperglycemia and in defective cerebral circulation.

Tachyrhythmia is generally thought to be due to irritation and excitations of various origins.

Hypersynchrony is apparently caused by a large number of neurons discharging electricity excessively at the same time. Paroxysmal, hypersynchronous discharges are the outstanding electroencephalographic feature of the epilepsies.[6] An epileptic

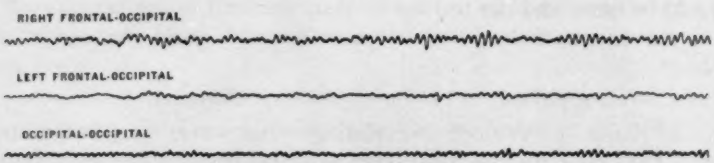

Fig. 1.—Normal electroencephalogram.

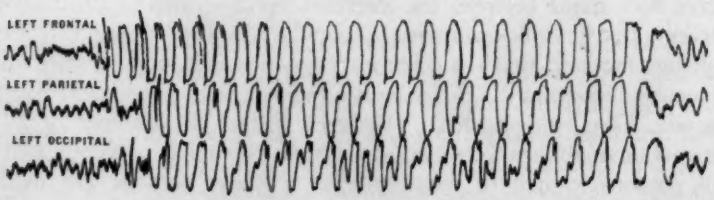

Fig. 2.—Complete petit mal seizure.

seizure can truly be called an actual "brainstorm." Without knowing anything about the brain's electrical activity, Jackson wrote in 1870 about "occasional, excessive discharges" causing convulsions.[2b] With the newer knowledge of brain waves epileptic seizures should be defined as abnormal conditions produced by paroxysms of excessive neuronal discharges within the brain, without regard to the cause and the immediate exciting mechanism.

Idiopathic epilepsy is electrographically characterized by the excessive discharges occurring periodically, bilaterally symmetrically and in all leads. The hypersynchronous waves may be abnormally fast or abnormally slow, or the two types of waves may be combined. The grand mal seizure manifests itself by a succession of high spikes; the typical petit mal seizure is pictured by alternating spikes and 3 per second waves. In the seizure-free periods these epileptic patients may show a 3 per second wave and spike pattern [7] too, but more frequently just periods of 3

6. Jasper, H., and Kershman, J.: Electroencephalographic Classifications of the Epilepsies, Arch. Neurol. & Psychiat. **45**:903 (June) 1941.

7. Hyland, H. H.; Goodwin, J. E., and Hall, G. E.: Clinical Applications of Electroencephalography, Canad. M. A. J. **41**:239 (Sept.) 1939.

to 4 per second waves, especially after hyperventilation.[8] These paroxysms of symmetric 3, 4 and even 6 per second waves are also characteristic of the so-called epileptic equivalents of epileptoid subjects and are found in many behavior disorders.[9] They are common in relatives of persons with epilepsy who have never had clinical seizures. These are the epileptic manifestations that are inherited and should be looked for from the standpoint of genetics.

Organic disorders can at times closely resemble idiopathic epilepsy in their electrographic records. Localized lesions of the brain, if they involve the superficial structures to a sufficient degree, will be recognized by the occurrence of abnormal waves in that one particular area only.[10] In temporal, rarely in other, localizations, unilateral tumor can cause disturbances of the normal rhythm on both sides. Diffuse diseases, such as encephalitis, degeneration and congenital anomalies, can be recognized as diffuse through the appearance of their electroencephalographic characteristics all over the brain with a fairly even degree.

The electroencephalograph has been used on patients with injuries to the head by many examiners, especially in Great Britain. Most of these investigators have found that the severity of the electroencephalographic disturbances runs approxi-

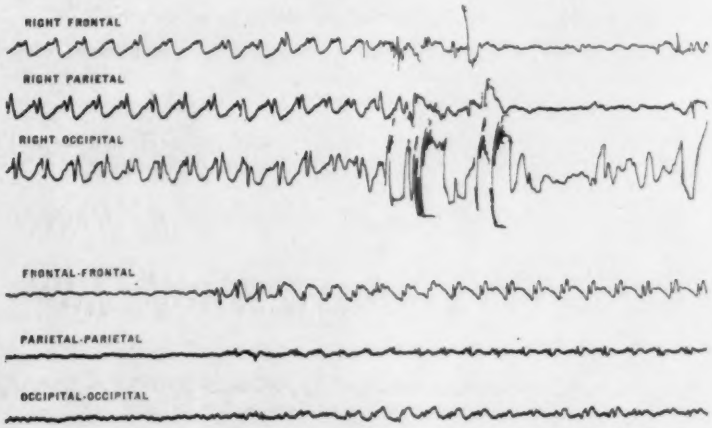

Fig. 3.—Beginning and end of petit mal seizures.

mately parallel to the severity of cerebral concussion and can be used as an index to show the progress of the patient.[11] Slow waves and dysrhythmias usually stay much longer than symptoms persist.

RESULTS

Between Oct. 1, 1941 and Oct. 1, 1942, 73 electroencephalograms were made on 67 patients of this hospital and its outpatient departments. The examinations were performed with a three channel Rahm electroencephalograph in the department of roentgenology of Milwaukee Hospital (Dr. H. W. Hefke, head of the department). All but 2 patients were examined with six active and two inactive electrodes in fifteen leads; on 1 patient eight scalp and no ear electrodes were used and on another only four active and two inactive ones.

8. McEachern, D.: Epilepsy, Canad. M. A. J. **45**:106 (Aug.) 1941.

9. Lindsley, D. B., and Cutts, K. K.: Electroencephalograms of "Constitutionally Inferior" and Behavior Problem Children, Arch. Neurol. & Psychiat. **44**:1199 (Dec.) 1940.

10. Bennett, A. E.: The Value of Electroencephalography in Neurology, Nebraska M. J. **27**:239 (July) 1942. Penfield and Erickson.[2b] Davis.[4]

11. Gibbs, F. A.: Diagnostic and Prognostic Value of the Electroencephalogram, J. A. M. A. **118**:216 (Jan. 17) 1942.

The 67 patients were classified according to their clinical diagnosis before being referred for electroencephalography. All children with typical or strongly suggestive petit mal seizures and children with generalized convulsions in which no other causes for the attacks had been found previously were classed as having clinically idiopathic epilepsy. The electrographic interpretation of idiopathic epilepsy was based on the finding of runs of bilaterally symmetric, hypersynchronous waves of 6 per second, 4 per second and 3 per second and the 3 per second wave and spike pattern in all leads, appearing with or without hyperventilation. Children with the so-called "psychomotor seizures" of Gibbs were classed in this group too. Deep breathing of three minutes or more was attempted by all patients, but a large percentage of the children did not cooperate adequately on this point, as could be

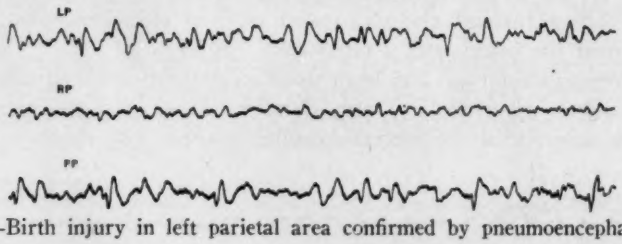

Fig. 4.—Birth injury in left parietal area confirmed by pneumoencephalogram.

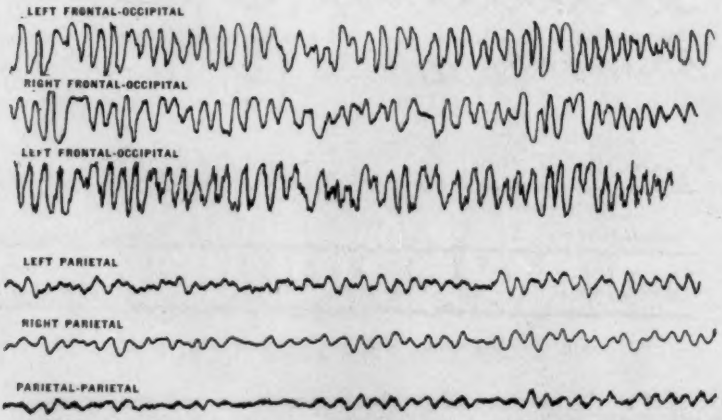

Fig. 5.—Diffuse cerebral degeneration; least disturbance in the parietal areas.

expected with an age group between 23 months and 14 years. Almost all suspected children with normal tracings had refused to hyperventilate.

The condition of 50 patients had been clinically diagnosed as idiopathic epilepsy. Twenty-six of these 50 children, i. e. 52 per cent, showed a typical epileptic pattern on the records with or without hyperventilation. For 5 patients clinical petit mal seizures were recorded. Thirteen children with a diagnosis of epilepsy, i. e. 26 per cent, had normal tracings; at least 2 of these had been given sedatives freely in spite of orders to the contrary; 4 patients in the epileptic group had definitely abnormal electrographic tracings, with random, high, slow waves in various leads, and could not be grouped into any one established diagnostic entity. Four other children that had had generalized convulsions for several years showed diffuse, high 3 and 4 per second waves throughout, without any epileptic pattern; these diffuse cortical disturbances might be secondary to repeated epileptic seizures or might be due to congenital anomalies or diffuse degeneration caused by other diseases. Two of

these 4 children were mentally mildly deteriorated; 1 had progressive deafness and congenital anomalies of the external ears and displayed temper tantrums; 1 little Negro boy in this group had his first convulsion three weeks after apparent recovery from chickenpox and had congenital anomalies (club feet, six toes).

Five of these 50 children had definite, localized electroencephalographic disturbances; 2 of these 5 patients had started to have seizures within six months of birth and were subsequently classed as having received injuries at birth, although their pneumoencephalograms were normal. The other 3 children had no pneumoencephalograms.

The remaining 17 patients fall into 11 groups according to their clinical diagnosis or symptoms.

Two patients were referred because of episodes of headaches of long duration; the tracings of these 2 children were normal.

One child was examined one month after a drained abscess of the brain had healed; the electroencephalogram localized the lesion correctly.

Two boys that had been hit by cars and suffered fractures of the skull had definitely abnormal tracings. A. C. was examined one year after he had sustained

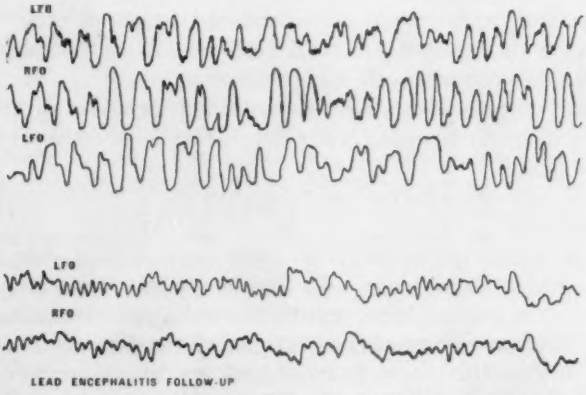

Fig. 6.—Lead encephalitis before discontinuation of exposure and after improvement.

a left frontotemporal fracture with subsequent decompression for a subdural hematoma; he had mild diffuse disturbances in the form of slightly hypersynchronous, slow waves in the entire left hemisphere with extremely high and slow waves and some sharp waves in the left frontotemporal area. The other boy, J. S., was first seen one month after surgical treatment for a compound depressed fracture of the skull in the right parietal region, causing a weakness of his left extremities. At that time, he had random, slow waves over the entire right hemisphere of the cerebrum, most pronounced in the parietal area. On reexamination after ten months, at which time all clinical residuals had disappeared, only mild diffuse disturbances could be found on the affected side, but in the right parietal region there occurred frequent episodes of high spikes with unusually high, 3 per second waves.

Two children were brought in because of severe progressive behavior disorders; while the girl's electroencephalogram did not reveal any abnormal conditions, the boy had a typical petit mal pattern.

For 2 girls a diagnosis of lead encephalitis had been made. No history of exposure to lead could be obtained for the 1 patient, but the roentgen findings in the long bones and the high level of lead in the urine had suggested this disease as

the cause of repeated afebrile convulsions; the electroencephalogram of this patient was normal. The other girl had had definite, prolonged exposure to lead paints at home; her father had had lead poisoning, and her long bones (on roentgen examination) and her urine suggested lead poisoning. The electroencephalogram constantly showed high, 3 per second waves in all leads. The exposure to lead was discontinued, and the electroencephalogram and the roentgenograms were repeated after four months. The lead lines at the epiphyses of the long bones had disappeared entirely in that interval, and the electrogram showed few, random, slightly hypersynchronous, 3 and 4 per second waves.

One child with known birth injuries, one-sided (right) convulsions and slight unilateral spasticity had abnormal manifestations in the left parietal region, confirmed by an area of atrophy in the left parietal area on a pneumoencephalogram.

One boy with headaches, central scotoma and contraction of the visual fields had a normal electroencephalogram.

Two patients were examined a few weeks after a cerebral concussion. One tracing was normal; the other showed some random slow waves with normal voltage that were more likely due to a cerebral deficiency than to a concussion, considering the minimal trauma and the fact that all children in that family, including this patient, were mentally slow and had speech defects.

Two patients with a probably normal personal history but a strongly epileptic family history had the typical petit mal pattern.

One boy with general muscular weakness and paralysis of the left abducens nerve of as yet unknown origin had a normal tracing without hyperventilation. His mother was epileptic.

Only 1 of 67 patients was too uncooperative for a satisfactory reading of the electroencephalogram.

Among the 67 patients examined there were three pairs of siblings. Brothers F. were clinically both epileptic; the elder had a typical petit mal pattern, but the younger brother, who refused hyperventilation, had a normal tracing. Brothers Fl. were both clinically and electroencephalographically epileptic. Sister T. was clinically epileptic; her brother, who had not had any known seizures, showed more severe electroencephalographic disturbances than his sister.

SUMMARY AND CONCLUSIONS

A short outline of the history, technic, importance and characteristics of electroencephalography is given.

A report on 73 electroencephalograms made on 67 patients of Milwaukee Children's Hospital gives a general idea of the value of this procedure in determining the causes and types of convulsions in children.

Electroencephalography is of definite value in studying convulsive and allied disorders. It represents a big step toward solving many of the problems associated with epilepsy and will be of great help if one remembers that it, like other diagnostic methods, has its particular indications and limitations.

Milwaukee Children's Hospital.

CONGENITAL IDIOPATHIC CARDIAC HYPERTROPHY

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In 1899 Simmonds [1] reported the first case of congenital idiopathic cardiac hypertrophy. Since then, a total of 77 cases similar in many ways to Simmonds' case have been reported.

In 1933 Kugel and Stoloff [2] extensively reviewed the literature up to that time and added 7 cases of their own. It was pointed out by them that in their cases etiologic factors, such as severe pertussis, tuberculosis, pneumonia, bronchitis, undeveloped fetal glomeruli, status lymphaticus with thymic enlargement and nephritis, made the idiopathic portion of this diagnosis untenable. The present case fulfils the clinical criteria for the diagnosis of congenital idiopathic cardiac enlargement, but on pathologic study syphilis was found to be an underlying factor, which, therefore, would exclude it from being an instance of true idiopathic hypertrophy.

REPORT OF A CASE

A white girl aged 13 months was admitted to the pediatric service of the Cumberland Hospital on Nov. 21, 1935 with reported anorexia, vomiting and dyspnea of two days' duration. The family history revealed a syphilitic father, who had been treated for syphilis at the board of health in 1934. The mother gave no history of any abortions or premature labor, the present child being the result of the third pregnancy and the third normal delivery. The birth weight was 5 pounds and 1 ounce (2,296 Gm.). Except for occasional mild colds, the development of the child up to two months previously had been entirely normal. At that time, the child manifested symptoms similar to those of the present illness; these lasted several days, after which she apparently fully recovered. Two days before admission, however, the same symptoms reappeared.

Physical Examination.—On physical examination, the patient appeared cyanotic, dyspneic and acutely ill. The pupils were equal and fixed in mid-dilatation. The lungs showed dulness in the left axilla and the upper right posterior portion of each lung. There were no rales. The heart was enlarged; the sounds were regular, rhythmic, rapid and of good quality, with no murmurs. The liver and spleen were both palpable. No abnormal reflexes were elicited. The temperature ranged between 98 and 100 F.; respirations averaged about 45 per minute, with a pulse rate of 140. The hemoglobin content was 70 per cent (Dare). The red blood cells numbered 4,300,000 and the white cells 20,300 per cubic millimeter; the differential count showed polymorphonuclear leukocytes 42, lymphocytes 55 per cent and monocytes 3 per cent. The urinalysis disclosed nothing abnormal. The Wassermann reaction of the blood was 4 plus. The spinal fluid showed no abnormal changes, and its Wassermann reaction was negative. The carbon dioxide content of the blood was 48 volumes per cent. Cultures of materials from the nose and throat revealed no pneumococci or Klebs-Loeffler bacilli. A roentgenogram of the heart revealed a large and globular cardiac shadow which suggested a congenital lesion.

On the second day in the hospital, the child became increasingly comatose and dyspneic. The pulse became slow and irregular and the heart sounds feeble. A moderate amount of abdominal distention was present. On the same day she was put into an oxygen tent. The child's condition grew rapidly worse, and she died on the morning of the fourth day in

From the Cumberland Hospital Department of Pathology.

1. Simmonds: Ueber congenital primäre Herzhypertrophie, Deutsche med. Wchnschr. **25**:425, 1899.

2. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infants and Young Children, Am. J. Dis. Child. **45**:828 (April) 1933.

the hospital. The final diagnoses were congenital idiopathic cardiac hypertrophy, infection of the upper respiratory tract and pneumonia.

Postmortem Examination.—The body was that of a well developed, undernourished girl of 13 months. The peritoneal, pleural and pericardial cavities were normal. The heart weighed approximately 125 Gm. The right auricle was dilated and its wall slightly thickened. The right ventricle was greatly dilated and its wall thickened to three times its usual width. The left auricle and ventricle were slightly dilated and the wall moderately hypertrophied. The foramen ovale permitted the passage of a small probe. The coronary sinuses and arteries were normal. The valves and their components were normal. The large vessels were normal with the exception of the pulmonary artery, which showed thickening and

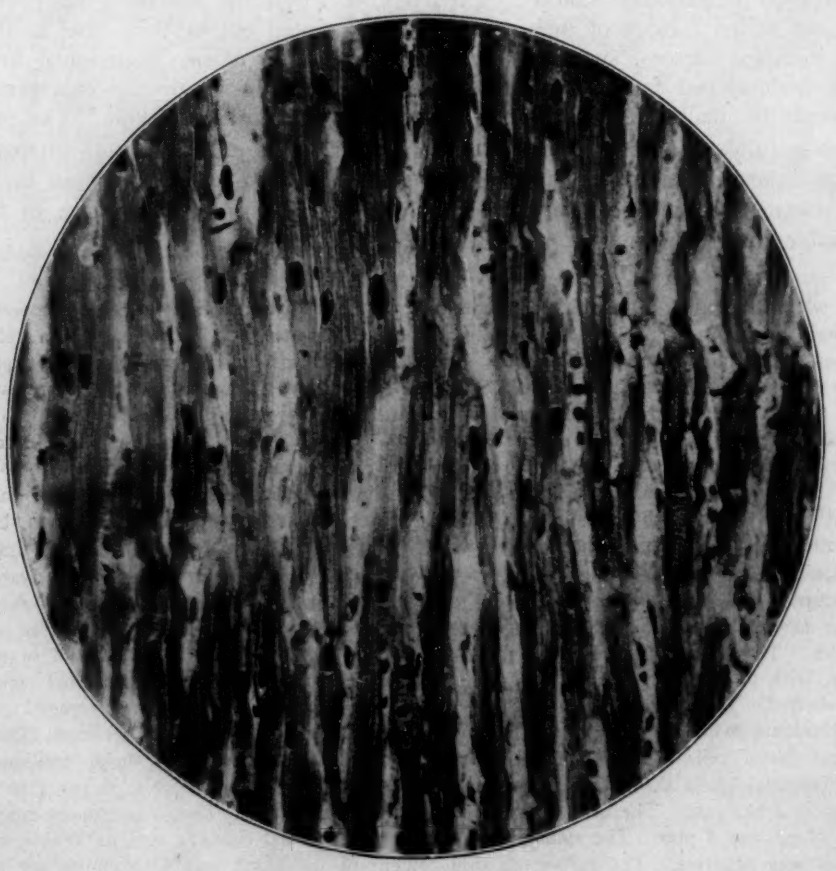

Fig. 1.—Section of a representative area of myocardial hypertrophy. Note the large nuclei and muscle cells.

sclerosis. Microscopic examination of the heart revealed pronounced hypertrophy of muscle bundles and an increase in the interstitial tissue, and many of the muscle fibers were edematous. The interstitium contained areas of cellular exudate, consisting essentially of round cells (fig. 1).

Grossly, the lungs were pale. On section, small areas of consolidation were present in the base of each lung. The pulmonary vessels were severely sclerotic and stood out from the cut surface like goose quills. Microscopically, the predominant cell of the infiltrate was of the mononuclear variety.

The liver weighed 310 Gm. It sectioned easily, and near the surface there were occasional collections of white pinpoint areas. The parenchyma appeared somewhat congested. Microscopically, in numerous fields the normal architecture was completely lost, owing to extensive

infiltration of the periportal spaces by mononuclear cells and replacement of the central portion of the liver lobules by fat. Occasional collections of infiltrate were also found replacing a large portion of the parenchyma of the liver (fig. 2).

The kidneys weighed 20 Gm. each. The capsules stripped with ease, revealing on each a lobulated, pale, smooth surface. The parenchyma and pelves were normal grossly. Microscopically, subcortical collections of mononuclear leukocytes with an occasional polymorphonuclear leukocyte and plasma cell were found throughout the sections. Similar lesions were found also in the medulla and pelvis. The tubules showed cloudy swelling (fig. 3).

The lymphatics and the endocrine glands were normal.

Fig. 2.—Section of the liver showing (*A*) periportal infiltration with mononuclear cells; (*B*) fat replacing the central portion of the hepatic lobules, and (*C*) large collections of mononuclear cells replacing the parenchyma of the liver.

The epiphysial zone of the humerus was moderately widened and showed a yellowish discoloration, apparently due to congenital syphilis.

The final anatomic diagnoses were: (1) congenital syphilis; (2) cardiac hypertrophy and dilatation; (3) sclerosis of the pulmonary artery (syphilitic), and (4) lobular pneumonia (terminal).

CONCLUSION

Another case is here recorded in which the clinical criteria for congenital idiopathic cardiac hypertrophy are fulfilled. When a clinician observes a baby with

a roentgen shadow of the heart occupying an enormous area in the chest cavity with no valvular or congenital lesion to which it might be secondary and when also certain symptoms appear, including respiratory distress accompanied with cyanosis and rapid and violent heart action, an entity comes to mind which he has been taught to recognize as congenital idiopathic cardiac hypertrophy. No treatment other than symptomatic has been considered, and the condition is known to be fatal. In this instance, however, the autopsy revealed the stigmas of congenital syphilis. In this connection, the pulmonary vascular lesion caused

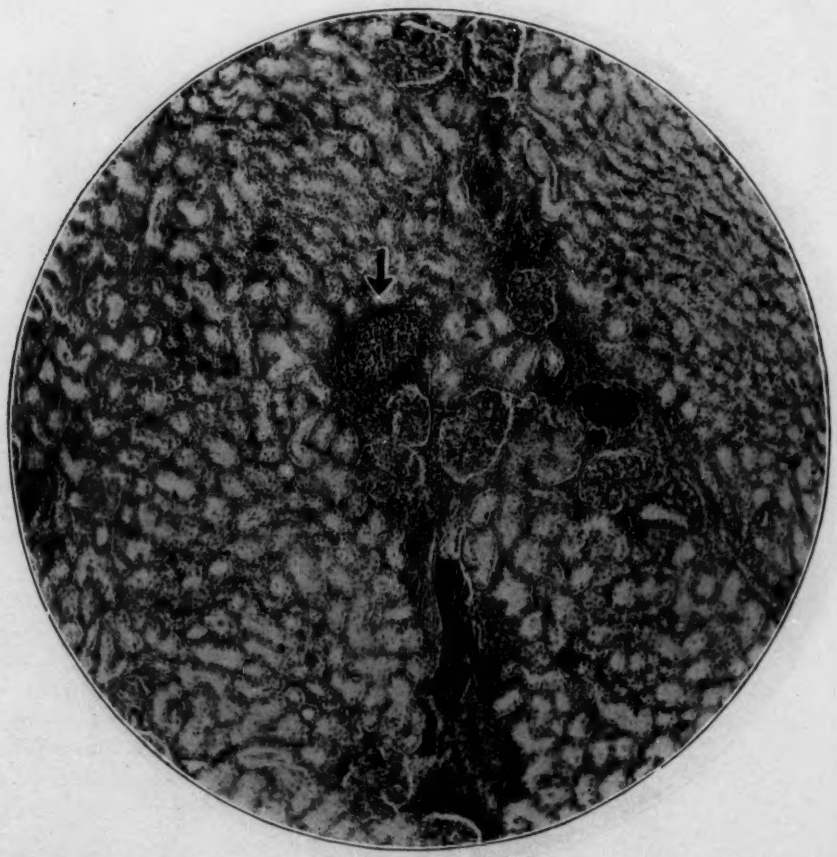

Fig. 3.—Section of a kidney, showing the characteristic collections of mononuclear cells in the cortex of the organ. The arrow points to one of these.

mechanical obstruction to the circulation, and this sheds ample light on the problem of the cause of the cardiomegaly. My experience in this case in conjunction with a review of the literature on the subject leads me to believe that there is no idiopathic congenital cardiac hypertrophy and that for this child at least a rational therapy was available.

Silik H. Polayes, Department of Pathology Cumberland Hospital, assisted in the preparation of this report.

85 Eastern Parkway.

ENZYMATIC DEBRIDEMENT IN THE LOCAL TREATMENT OF BURNS

A PRELIMINARY REPORT

GERALD R. COOPER, PH.D.

G. B. HODGE, M.D.
AND
J. W. BEARD, M.D.
DURHAM, N. C.

A problem of major proportions in the treatment of the secondary aspects of the deeper burns is the presence in the burned area of devitalized or injured tissues. The tissues involved depend on the site and depth of the burn, but for practical purposes the chief component for consideration consists of a mass of interlacing collagen fibers which extend throughout the dermis to connect with like material in the subcutaneous tissue and between the muscle fibers. The material, whether treated with severe coagulatory agents, simple ointments or wet dressings, forms a strongly adherent layer which separates but slowly from the tissues beneath. This layer constitutes a serious impediment to management of the case. Infection is liable to develop within the material or beneath it. Further, even if infection does not occur, the layer may impede healing and preparation of the area for skin grafting. It would appear that occasions might arise in which rapid removal of the eschar or devitalized layer would be desirable. Experiments have been made to learn whether an enzyme preparation might be developed suitable for this purpose, and the object of this paper is the description of such a solution which thus far exhibits promise as a chemical debriding agent of value in the treatment of burns and possibly of other conditions.

Experiments were made in vitro from the point of view of finding a chemical solution possessing the capacity to disintegrate or loosen the eschar or devitalized tissue from the burned area. Attention was directed chiefly to reagents likely to affect collagen, a protein highly resistant to proteolysis and to the usual protein solvents. Many of the ordinarily available proteolytic enzymes were examined, including pancreatin, papain and pepsin derived from both swine and shark, and the effects of added activators, denaturants and penetrants were studied. The test object for the in vitro experiments consisted of squares of whole thickness guinea pig skin, both burned and not burned. Very promising results were obtained with two solutions. One contained the enzyme, papain, in 2 per cent concentration in the presence of the activator, cysteine hydrochloride (0.4 per cent), and the penetrant and denaturant, sodium salicylate (8 per cent); the other, papain (2 per cent) with guanidine hydrochloride (8 per cent) alone. Papain in the absence of activators and denaturants was relatively inactive. Since less cost and less probable toxicity would be expected with the solution containing the combination of papain with cysteine hydrochloride and sodium salicylate, most of the studies were made with this preparation. With it the fastest reaction rates were observed when the *p*H was about 6, while the total range of reaction was spread over the *p*H scale between 4 and 9.5.

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Studies on the action of the papain-cysteine-salicylate preparation on the eschar or devitalized tissue have been made in 6 cases of burns. In 4 instances tannic acid and silver nitrate had been the original local treatment; in 1 the area had been treated with sulfadiazine spray, and in the other the area had been treated with triple dye (gentian violet 1.5 per cent, brilliant green 1 per cent and acriflavine 0.75 per cent in water. Application of the papain solution was

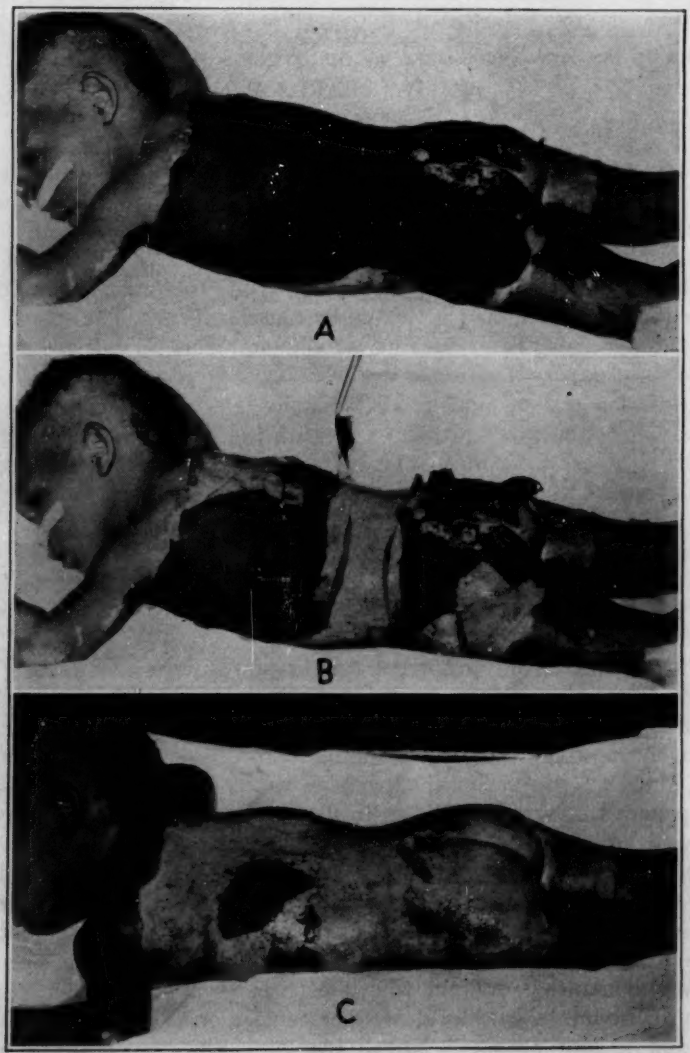

Fig. 1.—*A*, photograph taken sixty hours after treatment with tannic acid and silver nitrate and exposure for ten hours to the papain-cysteine-salicylate solution. *B*, photograph taken a few minutes after *A* to illustrate the loosening of the eschar, which came away in broad sheets. Note the glistening, healthy epithelium where the eschar was removed. *C*, photograph taken six days after *B*. Two small areas of eschar remain, and rapid epithelization is grossly apparent.

made by means of compresses saturated with the solution applied at intervals of thirty minutes.

The action of the enzyme in the patients treated with tannic acid and silver nitrate is illustrated by the results shown in the figure.

The patient was a Negro girl, 2 years of age, who had been burned over the whole of the back of the trunk as the result of falling into a basin of boiling water. She was brought to the hospital twenty-four hours after the accident. After debridement, the area was treated with 5 per cent tannic acid and 10 per cent silver nitrate. Sixty hours later, compresses of the enzyme solution were applied to the eschar. The appearance of the eschar in situ on removal of the compresses after ten hours' exposure to the solution is shown in *A* in the figure. In this photograph it is seen that the eschar was wrinkled and detached from the underlying tissues about the edges. The eschar was then picked up with forceps and cut across with scissors, coming away freely in the broad sheets laid back for illustration in *B*. The procedure was painless, as can be seen by the child's expression. The burn was wholly second degree, and the area showed throughout the presence of healthy-looking papillary epithelial islands. Two patches of eschar remained attached posteriorly where pressure prevented the solution from reaching the eschar. The denuded area was covered with cod liver oil ointment without cloth dressings. The condition of the burned region after six days, when rapid epithelization had become grossly apparent, is shown in *C*. Results similar to these were seen in the other cases in which the initial local treatment was application of tannic acid.

Results as favorable as these were not observed when the burned areas had been treated with sulfadiazine or triple dye. A case similar to that just described but in which the damaged area had been treated locally with sulfadiazine was available for study. Here the burn in some areas extended through the dermis. Five days after application of the sulfadiazine, gross infection was seen in the eschar, especially near the edges. After six hours' exposure to the papain solution, there was evidence of progressive digestion of the devitalized tissues, but there was no indication that the eschar would be removable in sheets as in the case of tannic acid eschars. Removal of the eschar depended entirely on complete digestion, layer by layer, from the outside, for which many hours were necessary. Digestion of the eschar was finally complete after a total of twenty-five hours, but these results were not comparable with those seen in the patients initially treated with tannic acid. The action of the enzyme solution on the patient treated with triple dye was somewhat similar to that seen after initial treatment with sulfadiazine. The eschar was removed only by complete digestion of the whole thickness of the layer, which occurred slowly.

Papain has been suggested [1] before for use on suppurating lesions, though never in combination with suitable activators. The results thus far obtained indicate that the papain-cysteine-salicylate solution exerts a powerful proteolytic action in vivo even when applied by the relatively crude medium of compresses wet with it. There has been no evidence of action on the living tissue about the eschar. In the remarkably rapid loosening of tannic acid eschars and the somewhat slower digestion of the tenacious layer of eschars formed over burns treated with sulfadiazine or triple dye, the preparation provides a valuable means for the elimination of this source of infection. Actually, with this solution infection in the local damaged area becomes a negligible factor. A notable systemic effect of the action of the solution was a consistent rapid decline in temperature observed to parallel the removal of the eschar. After gross digestion had begun, within six to twelve hours after application of the solution, the temperature was observed to fall from as high as 105 F. to a normal level within the course of a day, whether infection had been present locally or not. This suggests the rapid neutralization of toxic materials or the removal of their source, but it is possible that the antipyretic action of the salicylate may have been a participating factor. It is obvious that this preparation may be useful in conditions other than burns. Further study of the problem will be undertaken as cases become available.

1. Glasser, S. T.: A New Treatment for Sloughing Wounds: Preliminary Report, Am. J. Surg. **50**:320 (Nov.) 1940.

Case Reports

BACILLUS PYOCYANEUS MENINGITIS FOLLOWING PNEUMOENCEPHALOGRAPHY

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Meningitis caused by Bacillus pyocyaneus, a rare and highly fatal disease, has occurred repeatedly as a complication of common diagnostic and therapeutic procedures employing puncture of the lumbar subarachnoid space. Though only 55 cases (table) of this disease have been reported to date, in no less than 20 the disease was the direct result of such a procedure.

This is the report of a fatal B. pyocyaneus meningitis following pneumoencephalography and a review of the literature pertinent to its occurrence. The

Summary of Reported Cases of B. Pyocyaneus Meningitis

Outcome	Number of Cases	Secondary to Sepsis	Primary (Without Sepsis)	Not Stated
Recovery	20 (36%)	3 (15%)	16 (55%)	1
Death	33* (58%)	18 (86%)	13* (45%)	2
Not stated	3 (6%)	.....	.....	3
Total	56* (100%)	21 (100%)	29† (100%)	6

* Includes the present case.
† Twenty-one of these, including the present case, followed lumbar puncture.

latter will indicate the variety of sources from which contamination has taken place and should serve as a warning of the very real dangers encountered in the nevertheless valuable procedures employing lumbar puncture.

Though B. pyocyaneus is usually saprophytic and when pathogenic usually benign, its presence as the etiologic agent of purulent meningitis spells a poor prognosis. The gross mortality in 52 cases (the end result in 3 of the 55 cases not being reported) was 58 per cent. When the meningitis was secondary to a generalized sepsis due to this organism the death rate was still higher, in 18 of 21 cases (85 per cent) the course terminating fatally. In 28 cases in which the meninges alone were infected (primary meningitis) but 12 of the patients (52 per cent) died.

Twenty cases of B. pyocyaneus meningitis complicating procedures which employ spinal puncture have been reported. Of these, 1 followed the intraspinal administration of tetanus antitoxin. Meningitis in this case developed after apparent recovery from tetanus.[1] In 11 cases the meningitis complicated diagnostic lumbar punctures after the initial taps had disclosed normal spinal fluid.[2]

From the Children's Neuropsychiatric Service, Cook County Hospital.

1. Chauffard, A., and Laroche, G.: A Case of Meningitis Pyocyaneus, Bull. et mém. Soc. méd. d. hôp. de Paris **41**:645-648, 1917.

2. (*a*) Sonnenschein, C.: Fatal Meningitis After Lumbar Puncture, Deutsche med. Wchnschr. **49**:881-882 (July 6) 1923. (*b*) Levy, I. I., and Cohen, A. E.: Pyocyaneus Meningitis

(Footnote continued on next page)

Wise and Musser [2e] in reporting 6 of these cases stated the belief that the infection was introduced by a mercury manometer which was used unsterile except for a 6 inch sterile tip near the lumbar puncture needle. Thus, spinal fluid which ran into the instrument during jugular compression flowed back into the subarachnoid space on release. In 7 cases the infection followed the administration of a spinal anesthetic.[3] In 5 of these the organism was recovered from the solution of sodium chloride used to dilute the anesthetic.[3a] In 1 case, as in our own, it followed pneumoencephalography.[4]

Since the prognosis of the common purulent meningitides has so remarkably improved with the advent of therapy with sulfonamide compounds, it is interesting to note the potentialities of these drugs in B. pyocyaneus infections. Soeters [5] in 1937 first reported a case in which sepsis due to this organism was treated with sulfanilamide and repeated blood transfusions with recovery. Stewart and Bates [6] treated successfully with this drug an infection of the gastrointestinal and urinary tracts. Helmholz [7] and Long and Bliss [8] mentioned the efficacy of sulfanilamide in clearing the urine of B. pyocyaneus. Schein [9] reported an osteomyelitis of the spine which occurred as a complication of a renal B. pyocyaneus infection and from which the patient recovered with sulfanilamide therapy.

The only patients with B. pyocyaneus meningitis treated with chemotherapy were 4 of the 6 whose cases were reported by Wise and Musser.[2e] These were all adults and were treated with sulfanilamide and spinal drainage. They all recovered. The initial dose of the drug was given intraspinally, intravenously or intramuscularly, the maintenance dose in all cases being but 1 Gm. administered orally three times a day. In all these cases the condition was correctly diagnosed in the first twenty-four to thirty-six hours, and the authors attribute the patients' recovery to the early institution of drainage.

REPORT OF A CASE

A. S., a 2 year old white girl, was admitted to the Children's Division of Cook County Hospital in December 1941 for diagnostic investigation of precocious sexual development. Her general health and development were good. There were no abnormal neurologic findings. After extensive work-up, including laparotomy and histologic study of the ovaries, without

After Lumbar Puncture, J. A. M. A. **85**:1968-1969 (Dec. 19) 1925. (*c*) Evans, F. L.: Primary Meningitis Caused by Pseudomonas Aeruginosa (Bacillus Pyocyaneus): Review of Literature and Report of Three Cases, M. Rec. **144**:111 (Aug. 5); 172 (Aug. 19) 1936. (*d*) Berger, E. H.: Primary Pyocyaneus Meningitis: Report of Case Ending in Recovery, Northwest Med. **37**:242-245 (Aug.) 1938. (*e*) Wise, R. A., and Musser, J. H.: Bacillus Pyocyaneus Meningitis: Report of Six Cases, New Orleans M. & S. J. **92**:145-151 (Sept.) 1939.

3. (*a*) Schlagenhaufer, F.: Pyocyaneus Infection After Spinal Anesthesia, Centralbl. f. Bakt. (Abt. 1) **59**:385-387, 1911. (*b*) Schneider, H.: Pyocyaneus Meningitis, Wien. klin. Wchnschr. **37**:65-67 (Jan. 17) 1924. (*c*) Shrewsbury, J. F. D.: B. Pyocyaneus Meningitis with Recovery, Brit. M. J. **1**:280-281 (Feb. 17) 1934.

4. Iwasaki, S., and Motinaga, H.: Meningitis Due to Pyocyaneus Bacilli Developing After Pneumo-Encephalography, Okayama-Igakkai-Zasshi **51**:1780 (Aug.) 1939.

5. Soeters, J. M.: Septicemia Due to Pyocyaneus Bacilli, Maandschr. v. kindergeneesk. **7**:74-81 (Nov.) 1937.

6. Stewart, W., and Bates, T.: Bacillus Pyocyaneus Infections: Case Treated with Sulphanilamide, Lancet **1**:820-821 (April 8) 1939.

7. Helmholz, H. F.: Bactericidal Power of Urine After Administration of Prontylin by Mouth, Proc. Staff Meet., Mayo Clin. **12**:244-245 (April 21) 1937.

8. Long, P. H., and Bliss, E. A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine, and Allied Compounds, New York, The Macmillan Company, 1939.

9. Schein, A. J.: Bacillus Pyocyaneus Osteomyelitis of Spine: Report of a Case of Successful Treatment with Sulfanilamide, Arch. Surg. **41**:740-746 (Sept.) 1940.

a cause for the disorder being found, it was decided that encephalographic studies be done to see if a silent tumor of the brain could be found.

On the afternoon of March 14, 1941 pneumoencephalography was done with the patient under anesthesia induced by avertin with amylene hydrate administered by rectum. Helium was introduced in the lumbar subarachnoid space by means of a 50 cc. syringe connected by 5 cm. of sterile rubber tubing to the lumbar puncture needle. The syringe was first filled with helium fed through a wash bottle connected to the tank by rubber tubing. The cerebrospinal fluid at the beginning of the procedure showed no cells. After the removal of 85 cc. of fluid and the introduction of 78 cc. of helium there were 31 lymphocytes per cubic millimeter in the last portion of fluid removed. (This pleocytosis following introduction of gases into the lumbar subarachnoid space occurs regularly and does not indicate a meningeal infection.[10]) The encephalograms were entirely normal. There was no unusual clinical reaction following the procedure, and the temperature, which rose to 101.8 F. at midnight, dropped to normal by early morning and remained there until her discharge. Though occasionally complaining of headache, the child ate well and retained all her meals. She was discharged March 19, afebrile and in apparently good health.

On March 24 she was readmitted to the hospital because of headache and inability to retain food or fluids. Her temperature was 101.8 F. and physical examination revealed nuchal rigidity and positive Kernig and Brudzinski signs. Lumbar puncture yielded cloudy fluid with 137 mg. of protein per hundred cubic centimeters. The spinal fluid sugar level was "too low to read." There were no organisms on direct smear, but cultures of the fluid from this as well as from two subsequent taps all yielded B. pyocyaneus.

The patient, weighing 31 pounds (14.1 Kg.), was given 2 Gm. of sodium sulfapyridine intravenously and 5.75 Gm. of sulfapyridine by mouth in the first twenty-four hours. Thereafter, the dose was 0.5 Gm. every four hours. Meningeal irritation persisted, and the next day there was clouding of the sensorium; but after three days of treatment she became afebrile and generally improved, remaining so for thirty-six hours. Coincident with a reduction in sulfapyridine to 0.25 Gm. every four hours, the temperature again rose and meningeal irritation increased. Even when the previous dosage of sulfapyridine was reestablished, her condition remained poor. The spinal fluid cell count varied between 1,000 and 5,000, with polymorphonuclear leukocytes predominating; protein levels were always high, but sugar thereafter remained at normal values. Meningeal irritation and fever gradually increased, and on April 12, nineteen days after her second admission, she died.

Autopsy confirmed the diagnosis of purulent leptomeningitis due to B. pyocyaneus. In addition, a hyperplastic abnormality of the tuber cinereum explained the sexual precocity. (This aspect of the case has been reported separately.[11])

In an attempt to locate the source of contamination, cultures were taken from the washbasin, the helium, the tank adapter, the rubber tubing, the wash bottle and the syringe. All cultures were negative except those from the sink and wash bottle, both of which yielded B. pyocyaneus.

Apparently the wash bottle had been contaminated or had not been properly sterilized, but it is interesting to note that encephalography was performed on another child at the same time and with use of the same equipment and procedure without apparent complications or sequelae.

It is evident that the organisms were introduced into the subarachnoid space via the helium which was contaminated in its course through the wash bottle. It is surprising in this connection that B. pyocyaneus infections are not more common in persons subjected to pneumoencephalography with air, since the usual procedure consists of simply aspirating atmospheric air into the syringe prior to its injection into the subarachnoid space. Since helium will not support the growth of organisms, it is felt that careful sterilization of the entire conduit system would permit the use of helium from ordinary container tanks without hazard of bacterial contamination.

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10. Levinson, A.; Kaplan, I., and Cohn, D. J.: Changes in Chemistry of Cerebrospinal Fluid During Encephalography, J. Lab. & Clin. Med. **25**:225-237 (Dec.) 1939.

11. Bronstein, I. P.; Luhan, J. A., and Mavrelis, W. B.: Sexual Precocity Associated with Hyperplastic Abnormality of the Tuber Cinereum, Am. J. Dis. Child. **64**:211-220 (Aug.) 1942.

This case, as well as the others reported in the literature, will serve to emphasize the importance of observing complete surgical asepsis in all procedures employing puncture of the subarachnoid space.

SUMMARY

A case of B. pyocyaneus meningitis following pneumoencephalography with helium is reported. Death resulted in spite of intensive sulfapyridine therapy. The source of contamination was a wash bottle through which the gas was passed. The literature on B. pyocyaneus meningitis and the chemotherapy of B. pyocyaneus infections is reviewed.

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CONGENITAL DEFECT OF THE SKIN IN A NEWBORN INFANT

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Congenital defect of the skin in the newborn is a comparatively rare occurrence. Not more than 125 cases have been reported. And of these it is interesting to note that the great majority were cases of lesions of the scalp. Thus in 1930 Terruhn's [1] review showed 76 cases in which the head was involved and 29 in which the rest of the body was involved. Since then there have been few reported cases.

Greig [2] described two forms of local congenital defects of the hairy scalp not involving the bone: one appearing as a bulla or raw surface and the other entirely membranous or cicatricial. The usual appearance is that of a deep, circular ulcer of varying size, either single or multiple, most common over the vertex of the skull but likely in any location. The lesion may be more extensive, as in Dowler's [3] case of a normal newborn infant with a scalp defect extending over the entire cranial vault from a point just in front of the anterior fontanel to the posterior fontanel. At the vertex there was a granulation tissue, while the rest of the defect had a fibrous and cicatricial consistency.

Lesions on the trunk or extremities, in association with scalp defects or independently, appear as ulcerations, or, more commonly, the absent skin is represented by a thin translucent or transparent membrane, through which the underlying structures are visible. There also may be areas of dense scar tissue, suggesting a lesion that has begun early in fetal life and has already undergone partial healing at birth.[4]

Though areas of deficiency or absence of skin may occur singly and anywhere on the body, it is usual for them to appear bilaterally and to be symmetric in size, shape and appearance. Distribution on the extremities is usually not great, but it may be extensive on the abdomen. Typical of the involvement of the extremities are cases described by Trillat and Cornut [5] in which in areas on the right forearm

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From the Abraham Jacobi Division for Children of the Lenox Hill Hospital, service of Dr. Jerome S. Leopold.

1. Terruhn, E.: Ueber die Entstehung amniogener Hautdefekte während der Schwangerschaft mit besonderer Berücksichtigung des Schädels beim Neugeborenen, Arch. f. Gynäk. **140**: 428, 1930.

2. Greig, D. M.: Localized Congenital Defects of the Scalp, Edinburgh M. J. **38**:341, 1931.

3. Dowler, V. B.: Congenital Defects of the Skin in a Newborn Infant, Am. J. Dis. Child. **44**:1279 (Dec.) 1932.

4. (*a*) Finkelstein, H.: Säuglingskrankheiten, ed. 4, Amsterdam, Elsevier, 1938, p. 120. (*b*) Adair, F. L., and Stewart, C. A.: Congenital Defect of the Skin of the Newborn, Am. J. Dis. Child. **27**:60 (Jan.) 1924. (*c*) Oing, M.: Schädelhautdefekte bei neugeborenen Kindern, Zentralbl. f. Gynäk. **53**:1522, 1929.

5. Trillat, P., and Cornut, P.: Absence congénitale de la peau sur l'avant-bras droit d'un nouveau-né avec aplasie musculaire et lésions osseuses, Bull. Soc. d'obst. et de gynéc. **25**: 257, 1936.

absent skin was replaced by healed scar tissue, and by de Vink,[6] whose case was that of a healthy newborn infant with symmetric, triangular cutaneous defects measuring 2 by 1 cm. on the inner aspects of the knees. The appearance was likened to that of a healing burn. Abt [7] reported the case of an infant with symmetric areas of defective skin 1 by ¼ inch (2.5 by 0.6 cm.) in size over each knee. The lesions were irregular and punched out, with raised and puckered edges.

More extensive areas involving the trunk are illustrated by the cases of Hahn,[8] Adair and Stewart [4b] and Dowler, in all of which the lesions were strikingly similar. A large U-shaped area, involving more than one-half the anterior and lateral abdominal walls and exhibiting various stages of repair, from a transparent layer of thin cicatricial tissue, through which muscle fascia could be seen, to a healthy scar, was described by Dowler. There was a coexisting defect of the greater part of the scalp, previously mentioned. In addition to the abdominal defect in Adair and Stewart's patient there were small cutaneous lesions, 2 by 3.5 cm. in extent, also present on the lateral aspect of each thigh and arm. Linear scars connected the smaller and larger areas, suggesting greater defects than at birth and some healing. Occasionally other anomalies are associated with defects of the scalp. Thus Oing [4c] described a case with coexisting harelip, cleft palate, deformities of the fingers and polydactyly.

The cause is not clear. The most frequently expressed opinion is that given by Abt [7] and others, of inflammatory adhesions between the external layers of the skin and amnion, at which points growth of flat epithelial cells is retarded, which causes an accumulation of liquor amnii and formation of Simonart bands. If these bands are torn loose from the integument of the fetus, a cutaneous defect remains. Terruhn has elaborated the theory of amniogenic defects during pregnancy in great detail, and he stated the belief that many cases can thus be explained. Von Reuss [9] expressed himself as being of a similar mind. Finkelstein suggested that those lesions which occur shortly before birth may be related to the tearing of amniotic bands, but he stated that others are better explained as developmental defects in the skin.

Punched-out ulcers suggested a trophic disturbance to Dowler, while Oing described 2 such cases of scalpular ulcerations with syphilis in a mother and infant, which she considered primary lesions. Neumann [10] reported 2 cases in which the Wassermann reactions of the mother were positive, but he did not consider the condition syphilitic. Trauma during vaginal examination has been mentioned as one of the less likely causes, but so many cases have occurred in which no examinations were made that this theory is untenable. Injury is further improbable as a cause, since many lesions appear so early in fetal life.

Greig rejected injury and amniotic adhesions as adequate etiologic factors because of the symmetry and size of the affected areas. These theories further fail to explain why the ulcerative type is invariably circular and why the same defect may occur in 2 successive children in the same family, as described by Campbell.[11]

6. de Vink, L. P. H. J.: Kongenitaler Hautdefekt bei einem Neugeborenen, Arch. f. Gynäk. **167**:291, 1938.

7. Abt, I.: Congenital Skin Defects, Am. J. Dis. Child. **14**:113 (Aug.) 1917.

8. Hahn, W. J.: Angeborener Defect eines grossen Theils der Haut des Rumpfes, J. d. Chir. u. Augenh. **30**:156, 1840.

9. Von Reuss, A. R.: Die Krankheiten des Neugeborenen, Berlin, Julius Springer, 1914, p. 342.

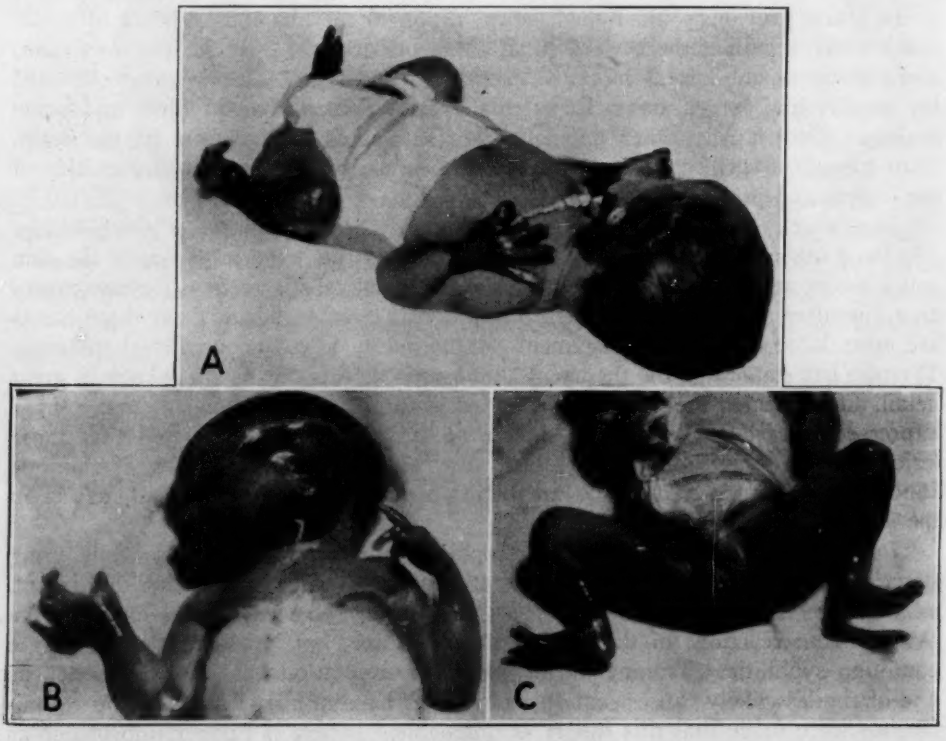
10. Neumann, H. O.: Kongenitale Hautdefekte am behaarten Schädel der Neugeborenen, Zentralbl. f. Gynäk. **48**:628, 1924.

11. Campbell, W.: Case of Congenital Ulcer on the Cranium of a Fetus, Edinburgh J. M. Sc. **2**:82, 1826.

De Vink stated the belief that the defect may be a recessive trait. The most satisfactory explanation is an arrest of development in the areas and structures involved.

Prognosis depends in great degree on the general condition of the patient and on the extent of the lesion. Cutaneous defects have been observed in stillborn infants, in infants who have lived only a few hours and in otherwise normal infants who have survived. Thus complete healing was noted in the cases of Abt, Dowler, Adair and Stewart and de Vink.

The treatment suggested by Tow [12] is the use of a dusting powder and sterile gauze dressing. Adair and Stewart employed a powder of equal parts of mild mercurous chloride and bismuth and a sterile gauze dressing impregnated with



A, distribution of areas of absent skin on the scalp and on the upper and lower extremities. *B*, absence of ear lobes and defect of the scalp, through which the underlying vessels may be seen and surrounding the ear above, posteriorly and below, extending down along the neck; also shown are defects of the left elbow, wrists and dorsum of hands and fingers. *C*, cutaneous defect of the lower extremities, somewhat more extensive on the left than on the right, but involving the legs and feet on both sides.

paraffin to prevent adherence to the oozing surfaces. More extensive lesions are best treated as one would treat a burn.

Our case presented some of the features which have been described by others and summarized in the foregoing paragraphs but differed in several respects. Most striking were the character and extent of the defect of the scalp, which involved almost the entire left parietal area and appeared similar to other lesions on the body rather than to the typical small circular ulcerations consistently

12. Tow, A.: Diseases of the Newborn, New York, Oxford University Press, 1937, p. 443.

described by other observers. The extensive distribution on the extremities was also unusual. The only associated anomaly of other organs was an absence of both ear lobes.

REPORT OF A CASE

On July 22, 1942 a girl was born one month prematurely, weighing 3 pounds 2 ounces (1,363 Gm.). The mother, aged 34 years, was well. Before pregnancy she had an anteverted, anteflexed uterus, the size and shape of which were within normal limits. The father had had pulmonary tuberculosis which had healed and was noncontagious. During the last month of the mother's pregnancy it became obvious that a polyhydramnios existed. At delivery more than 6 quarts (5.5 liters) of amniotic fluid was expelled. The delivery was otherwise spontaneous and uneventful.

The infant was perfectly formed except for numerous areas of absence of skin on the scalp, neck and extremities and absence of ear lobes (fig. *A*). Apart from those on the scalp, the areas of defective skin elsewhere tended to be symmetric. The missing skin in all areas was replaced by a thin, moist, glossy, transparent membrane, through which the underlying vessels and joints were clearly visible. The uncovered parts were a deep reddish brown. The hands and feet looked strikingly as if they were covered with rubber gloves. The scalp over the left parietal area was completely denuded, and the external auditory meatus was surrounded above, posteriorly and below by the large, circular uncovered area, which extended down along the lateral and mesial part of the neck in the shape of a question mark (fig. *B*). Both ear lobes were absent. The upper eyelids and the bridge of the nose were partially denuded. Other areas without skin were parts of the forearms and wrists, the dorsa of the hands and fingers and the lower extremities from the knee to and including the toes, which were completely uncovered (fig. *C*). On the forearm there were occasional small islands of epithelium, about ½ inch (1.3 cm.) in diameter, in the denuded area. The palmar surfaces of the hands were covered with normal skin. The heart and lungs were normal. Other examination revealed normal conditions.

Despite application of fluids and oiling, as well as application of external heat, the defective areas soon became dark brown and retracted, especially around the wrists, fingers, ankles and feet, which produced a macabre appearance. Toxemia and death occurred on the second day of life.

Postmortem examination by Dr. Rudolf M. Paltauf showed the gross defects already described. When the abdomen was opened the paniculus was thin and all the organs were found in their normal positions. No gross abnormalities were noted. The lungs were well aerated except for small areas of congestion and consolidation in the posterior portion of the lower lobe of each lung. The microscopic examination of the lungs showed a congestion and edema, partial atelectasis and a lobular pneumonia.

Sections of the skin through well preserved portions revealed all the layers—epidermis, dermis, corium and subcutaneous fibrofatty tissue—to be well developed. In the areas of apparent absence of skin the epithelium was reduced to a single row of cells. The corium was extremely thin and exhibited an occasional cluster of epithelial cells representing atrophic or undeveloped sebaceous glands. The subcutaneous fibrofatty tissue was reduced to a minimum.

SUMMARY

An unusual case of congenital defect of the skin of the scalp and extremities in a newborn infant is presented with a summary of the available literature. The most satisfactory etiologic explanation is felt to be an arrest of development in the structures and areas involved. Therapy and prognosis are discussed.

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LARGE CYST OF THE OMENTUM

ITS OCCURRENCE IN A THREE YEAR OLD CHILD

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Little has appeared in the pediatric literature in reference to cysts of the omentum, especially during the first few years of life. Because of the rarity of these formations, the diagnosis is usually not made until after the abdomen is opened. When such cysts do occur, they produce large abdominal tumors consisting of one or more cystic cavities lined with endothelium and filled with clear serous fluid. Attention is usually drawn to a tumor of this sort by the increasing abdominal distention and at times by dyspnea. The condition may resemble that of ascites. Surgical removal of these tumors should be done, and, as the growths are benign, they do not recur.

Recently we had the opportunity of seeing a 3 year old child with one of these large cysts of the omentum.

REPORT OF A CASE

R. M. W., a 3 year old white girl, was seen by one of us (M. H.) with a history of seeming perfectly well until the morning of May 3, 1942, when she began to complain of pain in her abdomen. Even with the pain she was up about the house playing with her toys. She had a normal bowel movement shortly after arising from bed. That afternoon she took a nap, and on awakening she seemed to be a little feverish. When her mother attempted to lift her out of bed the child complained of pain in the lower right side of her abdomen. She wanted to lie quietly in bed, and each time some one attempted to move her she cried out because of the pain in her abdomen. She was taken to the physician's office about 7 p. m. of the same day.

The child was born at term after a normal labor and delivery, weighing 7 pounds 8 ounces (3,400 Gm.) at birth. She was bottle fed, given a formula of pasteurized milk, water and dextrimaltose. She had always been in good health except for occasional colds and so far had not contracted any of the childhood diseases.

The mother and father were living and were in good health. There was 1 brother, 4 years of age, who was also in good health.

Physical Examination.—The rectal temperature was 101 F., the pulse rate 110 and the respiratory rate 30. The child was fairly well nourished. The nasal mucous membranes were slightly infected, but the tonsils were not enlarged or inflamed. The teeth were in fair condition. The anterior cervical lymph nodes were slightly enlarged bilaterally. The eyes and ears were normal. The chest was of normal contour, and respirations were regular; the percussion note was resonant throughout; the breath sounds were clear. The heart was of normal size, with muscle tone of good quality and rhythm regular. Of special note was the abdomen: With the child lying on the table it appeared to be distended, but when the mother was asked whether she had noticed this her reply was that the child had a high stomach and that it had been a matter of comment at home. On palpation the upper half of the abdomen was soft while the lower half seemed a little more resistant. The upper half was definitely tympanitic on percussion, while the lower half gave a dull to flat note. Peristalsis could be heard in the upper but not in the lower portion of the abdomen. The liver and spleen were not palpable. The extremities were normal. On rectal examination, a bulging mass, which seemed tender to the touch, could be felt especially to the right of the midline. The child was referred to the other of us (W. L.) at the Locust Mountain State Hospital, Shenandoah, Pa.

At the hospital her urine was found to be normal. The blood count showed: hemoglobin content, 79 per cent; red cells, 3,700,000, and white cells, 14,750. The differential count showed 16 per cent lymphocytes and 84 per cent polymorphonuclear cells, of which 60 per cent were

segmented and 24 per cent stab forms. Because of the large mass in the lower half of the abdomen it was decided to do an exploratory operation through a McBurney incision on the right side. When the peritoneum was opened, a tense, greenish cystic mass was apparent, which was composed of two parts. The mass was freed at many points by careful manual separation, and both of its parts were extracted through the original incision. The cysts were seen to have originated in the great omentum just ½ inch (1.3 cm.) from the attachment of the transverse colon. Most of the omentum had been obliterated, only a short apron near the transverse colon having been left. The omentum was tied off, and the cysts were enucleated. As the condition of the patient did not seem good, an attempt was not made to remove the appendix. It was felt that the added slight operative trauma might be serious and that the chance of infection would be greater without the presence of "the policeman of the abdomen." The wound was closed without drainage by use of chromic 0 catgut in the peritoneum and muscle and stainless steel wire in the aponeurosis and skin.

The postoperative reaction was severe; on the day of the operation the temperature was 103.2 F. and the pulse rate 168. On the following day the temperature and the pulse rate gradually came down, and the little girl had an uneventful convalescence, with the exception of an upset on the tenth postoperative day, when her temperature rose to 101 F. and she began to vomit. Hypodermoclysis of a dextrose solution was given, and the child responded well.

Pathologic Examination.—The specimen consisted of two large cysts, averaging 10 cm. in diameter. There were numerous small outpouchings from each main cyst. The cysts were filled with clear watery fluid. In the center of one of the large cysts was a small cyst, about 4 cm. in diameter. The cysts had thin walls, averaging 2 mm. in thickness. Microscopically the thicker portions of the wall showed fibrosis. Lining epithelial cells were not seen in sections.

Diagnosis.—The diagnosis of omental cyst was made.

SUMMARY

The case of a 3 year old girl with large omental cysts is reported.

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Progress in Pediatrics

NEWER CONCEPTS IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE

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We are presenting some of the newer criteria of diagnosis of congenital heart disease, as a result of which more precision in diagnosis has become possible. The excellent reviews of atrial septal defect by Roesler [1] and Bedford, Papp and Parkinson [2] and the reports of Gross,[3] Eppinger, Burwell and Gross,[4] and Touroff and Vesell [5] on patent ductus arteriosus have placed the clinical diagnosis of these conditions on a sound footing. During the past four years we have studied upward of 80 cases of congenital heart disease both clinically and by angiocardiography. In some cases, operative and postmortem data also were available. Visualization of the cardiac chambers during life after the intravenous injection of 70 per cent diodrast has permitted, in our opinions, a more accurate analysis of the cardiac contours and a clearer understanding of the disturbed cardiac physiology than were available previously. All of our patients were older than 4 years of age, which excluded from investigation many complicated anomalies inconsistent with prolonged life and of interest only from the anatomic viewpoint.

Because of our experience in angiocardiography, the subject will be classified here from the point of view of the roentgen configuration, but not with the intention of exaggerating the value of the roentgen examination. It cannot be emphasized too strongly that a complete diagnosis from this examination alone usually is impossible. The roentgen configuration may be entirely normal in the presence of marked abnormalities. Furthermore, the roentgen features of congenital lesions are not exclusive to these diseases. Nevertheless, this method of classification has proved convenient, and the cardiac configurations are grouped according to outstanding characteristics as follows:

1. Enlarged pulmonary artery segment of the cardiac contour
2. Normal or small pulmonary artery segment
   - A. With right ventricular enlargement
   - B. With left ventricular enlargement
3. Right aortic arch
4. Dextrocardia

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* Fellow of the Dazian Foundation of Medical Research.

The diodrast 70 per cent used in this study was supplied by the Winthrop Chemical Company, New York.

Delivered by Dr. Sussman as the Lippitt Memorial Lecture of the Mount Sinai Hospital, Milwaukee, at the Marquette University Medical School, Milwaukee, Wis., Jan. 22, 1943.

1. Roesler, H.: Interatrial Septal Defect, Arch. Int. Med. **54**:339 (Sept.) 1934.

2. Bedford, D. E.; Papp, C., and Parkinson, J.: Atrial Septal Defect, Brit. Heart J. **3**:37, 1941.

3. Gross, R. E.: Persistent Ductus Arteriosus and Its Surgical Treatment, in De Sanctis, A. G.: Advances in Pediatrics, New York, Interscience Publishers, Inc., 1942, vol. 1, p. 167.

4. Eppinger, E. C.; Burwell, C. S., and Gross, R. E.: The Effects of the Patent Ductus Arteriosus on the Circulation, J. Clin. Investigation **20**:127, 1941.

5. Touroff, A. S. W., and Vesell, H. A.: Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus, J. A. M. A. **115**:1270 (Oct. 12) 1940.

The present report will concern itself with a discussion of differential diagnosis of the lesions in each of the groups, particularly in regard to cyanosis, physical signs, circulatory dynamics and electrocardiographic and angiocardiographic appearances.

1. ENLARGED PULMONARY ARTERY SEGMENT

The pulmonary artery segment may appear prominent roentgenologically in the following congenital conditions: (*a*) atrial septal defect; (*b*) patent ductus arteriosus; (*c*) isolated pulmonic stenosis with dilated pulmonary artery; (*d*) idiopathic dilatation of the pulmonary artery, and (*e*) Eisenmenger's complex.

Clinical Features.—A history of recurrent or persistent cyanosis indicates the presence of a right to left shunt and suggests the diagnosis of Eisenmenger's complex. In atrial septal defect and in some unusual forms of patent ductus arteriosus occurring particularly in infancy, cyanosis may appear, but only under conditions of strain; it is not pronounced. In isolated pulmonic stenosis cyanosis is of late onset and moderate intensity. However, once it appears it is apt to be progressive. In all of the conditions in the group, there may be a certain diminution in cardiac reserve, as indicated by dyspnea on exertion and a slight bluishness to the lips. However, in atrial septal defect cardiac failure may be present more or less continuously, while it is rare in patent ductus arteriosus. On the other hand, subacute bacterial endocarditis is found frequently in association with patent ductus but is rare with uncomplicated atrial septal defect.

Physical Signs.—The physical signs accompanying atrial septal defect ordinarily are characteristic. The blood pressure may be low and the pulse pressure small. The heart is enlarged mainly to the left. The apex is displaced to the left, and the pulsation is forcible. Usually there is a heaving systolic pulsation over the wall of the chest. A systolic thrill and perhaps a diastolic shock may be found over the pulmonic area. A round decrescendo systolic murmur extending throughout systole, heard best over the pulmonic area and just below it, is characteristic (fig. 1 *B*). In the same region there may be a soft blowing diastolic murmur (Graham Steelle). At the apex, the murmurs of mitral disease may be heard. When the murmurs are recorded, the systolic murmur over the pulmonic area is found composed of low or medium frequency components. The murmur is of large amplitude, is decrescendo in type and extends throughout systole. The diastolic murmur when present is of low amplitude and is composed of very high frequency components. A greatly accentuated pulmonic second sound with an almost metallic quality is the rule. These murmurs probably are not due directly to the septal defect but rather to the dilated pulmonary artery with relative pulmonic stenosis and insufficiency. For this reason, the murmurs are not greatly different when idiopathic dilatation of the pulmonary artery is present except that murmurs at the apex are absent.

In patent ductus arteriosus, characteristically there is a continuous loud murmur with systolic accentuation at the pulmonic area, generally attended by a palpable systolic thrill (fig. 1 *A*). There may be a visible systolic pulsation in the second left interspace. The murmur is almost invariably harsh and not blowing. It has been described variously as a machinery, humming-top, mill-wheel or train-in-the-tunnel murmur. A harsh murmur limited to systole may be heard, but this is rare except in infants. It was encountered in only 1 of our cases. The murmur may be transmitted over the region of the left ventricle, and its systolic component often is audible over the carotid arteries. A systolic murmur over the jugular notch was audible in all of our cases. The pulmonic second sound is accentuated.

The pulse pressure is increased owing to a low diastolic pressure which occurs when there is a considerable aortic regurgitation into the pulmonary artery during diastole.

Isolated pulmonic stenosis with a dilated pulmonary artery is a rare anomaly. A thrill localized to the second and third left intercostal spaces or diffuse over the precordium is fairly frequent. A prolonged harsh, rasping or blowing systolic

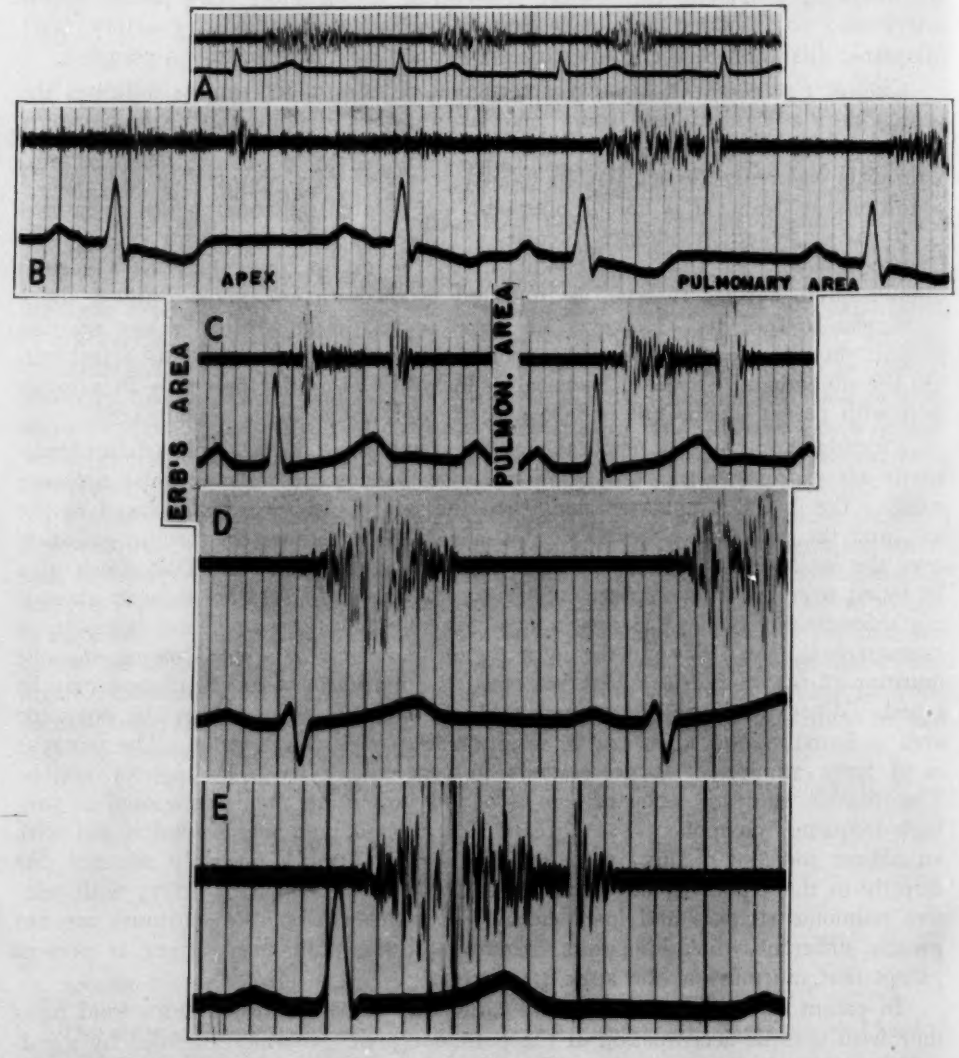

Fig. 1.—Phonocardiograms in various congenital lesions: *A*, patent ductus arteriosus; continuous systolic and diastolic murmur over the pulmonic area. *B*, Lutembacher syndrome; systolic and diastolic murmur with presystolic accentuation at apex; systolic murmur of high amplitude at pulmonic area and accentuation of second pulmonic sound followed by faint prolonged diastolic murmur. *C*, Eisenmenger complex; decrescendo systolic murmur of highest amplitude over pulmonic area with marked accentuation of second pulmonic sound. *D*, isolated pulmonic stenosis; systolic murmur of high amplitude and consisting of high frequency component over the pulmonic area; second pulmonic sound of low amplitude. *E*, congenital aortic stenosis; systolic murmur of high amplitude and consisting of high frequency component over the aortic area; second aortic sound of increased amplitude.

murmur maximum at the pulmonic area is present in most cases (fig. 1 *D*). In conus stenosis it may be lower, at Erb's area. It is transmitted upward along the course of the pulmonic artery and over the sternum but is faint or inaudible to the right of the sternum or at the apex. The pulmonary second sound is weak or absent in a certain proportion of cases, but it may be accentuated. A faint, short diastolic murmur may be found to the left of the sternum. The physical signs are not greatly different in the Eisenmenger complex except that in the latter a diastolic murmur at the base and along the left sternal margin has been reported. Nevertheless, in our 2 cases the diastolic murmur was not present (fig. 1 *C*). A diastolic thrill may be present. The pulmonic second sound is markedly accentuated and has a whiplike quality.

The electrocardiogram may be of considerable value in differential diagnosis in this group. Right ventricular enlargement, which is found regularly in pulmonic stenosis, atrial septal defect and Eisenmenger complex, is apt to be associated with right axis deviation, often of marked degree. Right bundle branch block is not uncommon. The QRS complex may be wide and notched. An abnormal increase in the amplitude of the P wave, with notching, is common. Prolonged PR intervals are not infrequent. T waves may be inverted in leads II and/or III. Auricular fibrillation is a feature only of atrial septal defect and is more often present when there is mitral stenosis or in older patients. In patent ductus arteriosus, on the other hand, extreme right axis deviation is unusual. The electrocardiographic changes in idiopathic dilatation of the pulmonary artery are not consistent, varying between normal and right axis deviation.

Circulation studies may be of interest. A delay in arm to lung and arm to tongue times is common in the conditions with right ventricular enlargement and in failure. However, when these time intervals are equal, a right to left shunt is indicated and in this present group of lesions suggests transposition of the great vessels, as it occurs in the Eisenmenger complex. When ether is used to determine the arm to lung time, paresthesias are noted in the extremities at the same time that the odor is detected on the breath of patients with a right to left shunt.[6] Occasionally this has been observed in a case of atrial septal defect, presumably being due to passage of some of the ether through the defect. There is no indication of a right to left shunt in any other member of this group.

Roentgen Examination.—The outstanding characteristic of the group is, of course, an enlarged, often bulging pulmonic segment at the middle left cardiac contour. The portion of the contour immediately below the pulmonary artery and above the left ventricle in the posteroanterior view ordinarily is concave. When the right ventricle and auricle are enlarged, as they are likely to be in all of the conditions in the group except patent ductus arteriosus, the diameter of the heart at the level of this concavity is widened and the junction of the right cardiac and supracardiac borders is elevated. Striking enlargement of the cardiac shadow to the right is not common except in the presence of failure. In the left oblique position, enlargement to the right and anteriorly is not marked. Enlargement to the left in the posteroanterior view, however, is common.

The dilatation of the pulmonary artery extends into the hilar vessels, which pulsate actively. When pulmonic insufficiency is present, organic or relative, regardless of the presence or absence of a murmur, the pulsation is of the collapsing type. This gives an appearance described as a "hilar dance" and is a feature of atrial septal defect. Although pulsation of the pulmonary artery in patent ductus arteriosus may be prominent, in our experience it is not collapsing.

6. Benenson, W., and Hitzig, W. M.: Diagnosis of Venous-Arterial Shunt by the Ether Circulation Time Method, Proc. Soc. Exper. Biol. & Med. **38**:256, 1938.

The absence of striking left auricular enlargement is a feature of the group. Gross [7] as well as Holman [8] has described left auricular enlargement in patent ductus arteriosus but not as a feature in the roentgen examination. There was significant esophageal displacement in 1 of 34 cases. Even in atrial septal defect, the esophagus may not be displaced. Indeed, when the esophagus is displaced posteriorly and compressed, as it is in mitral stenosis, a diagnosis of Lutembacher syndrome (stricture of the mitral valve associated with patent interauricular septum) is justified, provided simple mitral stenosis can be excluded.

Particularly in the conditions associated with enlargement of the right side of the heart, the aorta is apt to be small and the knob absent. The Eisenmenger complex is an exception, since in it the aorta is normal in size or dilated. In patent ductus arteriosus and in idiopathic dilatation of the pulmonary artery the aorta does not appear unusually small.

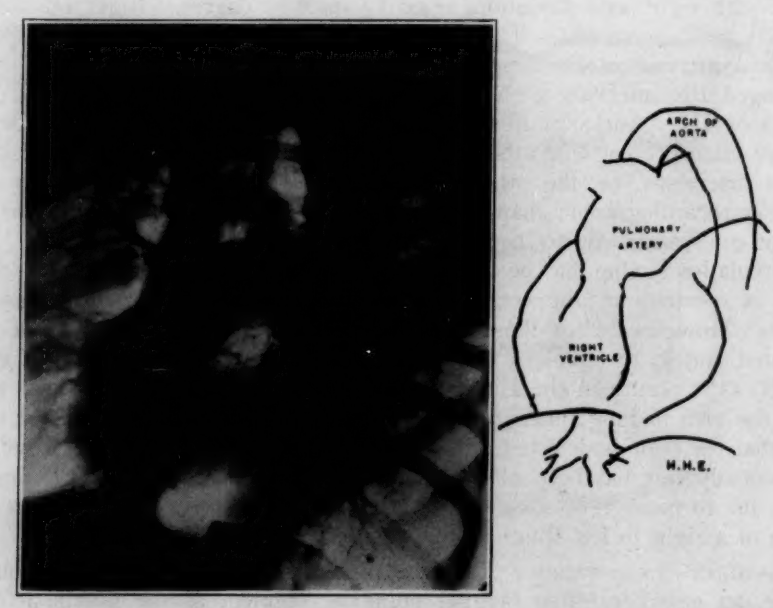

Fig. 2.—Eisenmenger complex in a boy of 16 years. Angiocardiogram (left oblique) made three seconds after injection shows opacification of the right side of the heart and a dilated pulmonary artery. The left ventricle and aorta are faintly but definitely opacified at the same time. There is no pulmonic stenosis. The right side of the heart is moderately dilated.

This discussion must not be construed as indicating that the pulmonary artery always is dilated in the conditions that are listed. This vessel has been enlarged, for example, in only 50 per cent of our cases of patent ductus arteriosus. Rare cases of atrial septal defect also have been reported without dilatation of the pulmonary artery. Pulmonic stenosis with a small pulmonary artery is discussed in a later section.

Angiocardiography is of great value in differential diagnosis. One of the most important contributions is the proof that a prominent pulmonic segment

7. Gross, R. E.: Surgical Closure of the Patent Ductus Arteriosus, Mod. Concepts Cardiovasc. Dis., December 1941, vol. 10.

8. Holman, E.: Arteriovenous Aneurysm: Abnormal Communications Between the Arterial and Venous Circulation, New York, The Macmillan Company, 1937.

actually is due to dilatation of the artery. Differentiation from mediastinal tumor and a normal-sized pulmonary artery distorted by a mediastinal process may be impossible by any other method.

In cases of the Eisenmenger complex, the procedure demonstrates unequivocally that the aorta receives blood from the right ventricle. The aorta is opacified within two seconds after injection, immediately after opacification of the right ventricle and simultaneously with visualization of the dilated pulmonary artery [9b] (fig. 2).

In atrial septal defect a shunt from right to left auricle is demonstrated occasionally by opacification of the left auricle immediately following that of the right. This is unexpected, since the left auricular pressure exceeds the right. The phenomenon is accounted for by the sudden introduction of a large quantity of diodrast into the right auricle, which rapidly, albeit temporarily, increases the pressure in this chamber. A left to right shunt ordinarily is to be anticipated and is demonstrated by continued opacification of the right auricle beyond the

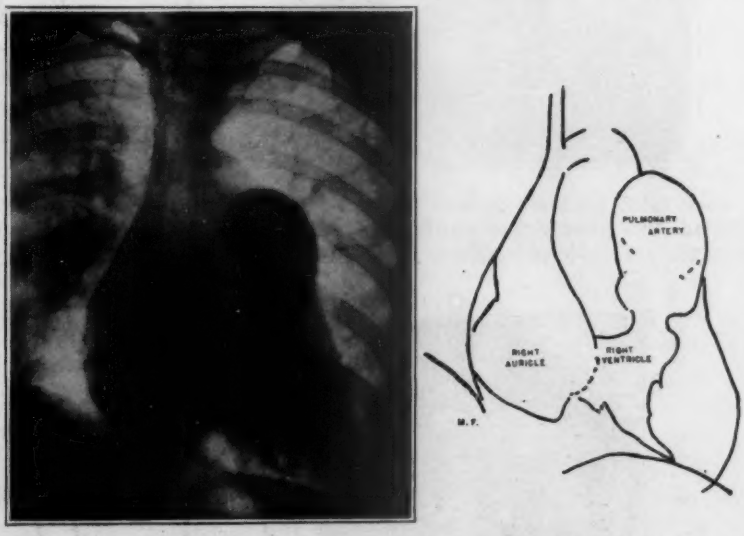

Fig. 3.—Lutembacher syndrome, in a 47 year old woman. Angiocardiogram (postero-anterior) made four seconds after injection shows a greatly dilated right side of the heart and pulmonary artery. The left auricle, visualized later, was only moderately enlarged.

time that it should be emptied. In practice, however, this demonstration often is not conclusive, because continued opacification of the right auricle may result when the injection is not sufficiently rapid or is not smooth or when, as a result of functional insufficiency of the tricuspid valve, the inferior vena cava or hepatic vessels are filled with diodrast, which they reempty into the right auricle. However, the method always provides a demonstration of extreme enlargement of the right side of the heart. Even in Lutembacher's syndrome, the dilatation of the right side of the heart dominates the picture and there is no striking displacement of the right chambers by the left auricle (fig. 3). This differs from simple mitral stenosis, in which the left auricular dilatation overshadows the right side of the

9. Steinberg, M. F.; Grishman, A., and Sussman, M. L.: Angiocardiography in Congenital Heart Disease: (*a*) I. Dextrocardia, Am. J. Roentgenol. **48**:141, 1942; (*b*) II. Intracardiac Shunts, ibid., to be published; (*c*) III. Patent Ductus Arteriosus, ibid., to be published.

heart and, in fact, displaces the right ventricle and pulmonary artery anteriorly and cephalad.[10a] The aorta is found to be normal in size or small.

A picture similar to that of atrial septal defect is obtained with isolated pulmonic stenosis. In this condition also the right side of the heart is very large. The pulmonary artery may be dilated. In addition, however, the stenosis of the pulmonary artery or conus is seen as an elongated narrowed segment replacing the region where ordinarily the pulmonic valve can be demonstrated. This

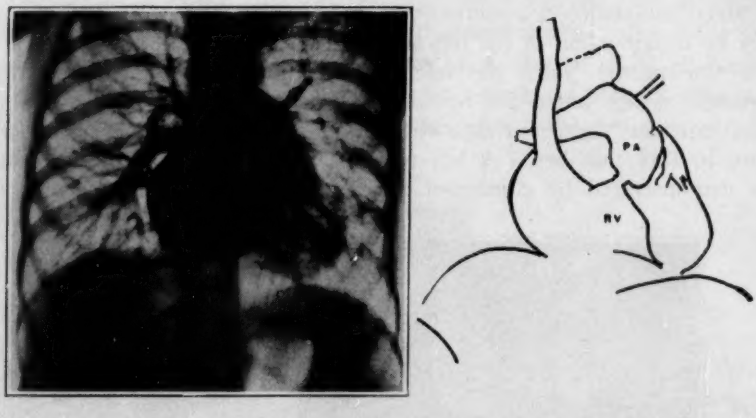

Fig. 4.—Isolated pulmonic stenosis in an 8 year old girl. Angiocardiogram (postero-anterior) made two seconds after injection showed enlarged right side of the heart, stenosed pulmonic conus and moderately dilated pulmonary artery.

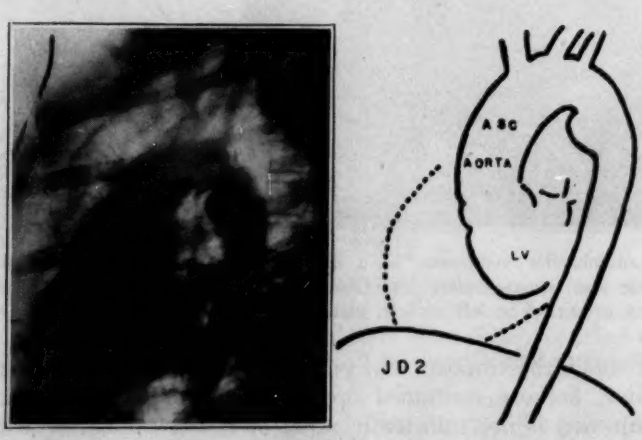

Fig. 5.—Patent ductus arteriosus (after ligation) in girl aged 12 years. Angiocardiogram (left oblique) made seven seconds after injection shows the entire aorta. There is a bulge in the contour of the proximal portion of the aorta descendens anteriorly which corresponds to the infundibulum of the ductus persisting postoperatively. Metal clips were placed adjacent to the ligated ductus at operation (Dr. A. S. W. Touroff).

demonstration usually is clear, because the concentration of diodrast in the right side of the heart and in the pulmonary artery ordinarily is good (fig. 4).

10. Grishman, A.; Steinberg, M. F., and Sussman, M. L.: (*a*) Angiocardiographic Analysis of the Cardiac Configuration in Mitral Disease, Am. J. Roentgenol., to be published; (*b*) Contrast Roentgen Visualisation of Coarctation of the Aorta, Am. Heart J. **21**:365, 1941; (*c*) Atypical Coarctation of the Aorta with Absent Left Radial Pulse, to be published.

Idiopathic dilatation of the pulmonary artery is suggested when pronounced enlargement of the pulmonic artery is not accompanied by the great enlargement of the right side of the heart that is characteristic of pulmonic stenosis.

Differentiation from patent ductus arteriosus can be made readily. The right side of the heart was not strikingly enlarged in our cases of the latter condition. In 50 per cent the pulmonary artery was dilated. However, in 26 of 27 cases the portion of the aorta just beyond the arch showed an abnormality in contour.[9c] Normally, the aorta is smooth in outline and there is a gradual diminution in the caliber from the arch to the descending portion. In patent ductus arteriosus, there is a bulge in the aorta just beyond the arch on the inner side of the curve. This is at the level of the ductus and probably represents the infundibulum of the ductus (fig. 5). In a few cases an aneurysm of the aorta due to traction by the ductus may account for the appearance. In most of the cases the left ventricle was found to be dilated in varying degrees.

2A. RIGHT VENTRICULAR ENLARGEMENT WITH SMALL PULMONARY ARTERY

The congenital lesions which fall into this category are the following: (*a*) isolated pulmonic stenosis with a small pulmonary artery; (*b*) tetralogy of Fallot; (*c*) cor biatriatum triloculare, and (*d*) transposition of the great vessels, with small pulmonary artery.

Discussion can be limited to two main lesions, isolated pulmonic stenosis and transposition of the great vessels. Cyanosis and clubbing are prominent and more or less permanent when transposition is present. In isolated pulmonic stenosis, cyanosis ordinarily appears late and is then usually progressive. Furthermore, the cyanosis is emphasized by factors which increase oxygen consumption, such as exertion.

Physical signs are apt to be similar. In pulmonic stenosis, there is a harsh systolic murmur and thrill in the second and third spaces on the left close to the sternum. The murmur is as a rule louder than that heard in the tetralogy of Fallot and is not conducted into the neck. In conus stenosis of the pulmonary artery, the murmur is placed slightly lower and is systolic in time. Its maximum intensity is in the fourth left space, close to the sternum. In the tetralogy of Fallot a thrill may be present, but not as commonly as in isolated pulmonic stenosis. A systolic murmur of less intensity may be heard over the entire heart but is maximum over the pulmonic area. It is transmitted into the vessels of the neck and may be heard in the left interscapular region. This is presumably due to the overriding aorta. On the other hand, when a large defect in the interventricular septum is present, resulting in cor triloculare, the murmur often is not transmitted and, indeed, may be absent entirely. The pulmonary second sound is diminished or absent.

Right axis deviation is characteristic of both lesions, unless complicated by a gross conduction defect. However, in pulmonic stenosis the axis deviation ordinarily is not so pronounced. P waves are often large and bifid. Circulation studies are important. In the tetralogy of Fallot the right to left shunt permits injected substances to enter the systemic circulation at the same time that they pass into the pulmonary circulation. These circulation times, therefore, although they may be prolonged, are equal. When ether is used, paresthesias are observed in the extremities. However, there are occasional cases of the tetralogy of Fallot in which signs of peripheral effects of ether are lacking.

Roentgenologically, the cardiac configurations may be similar, with an appearance described as a *cœur en sabot*. The heart is enlarged to the left, and the

apex is lifted. The pulmonary artery segment is small. The aorta is of normal appearance, or there may be, in the tetralogy of Fallot a dilatation of the ascending portion. In pulmonic stenosis, dilatation of the right ventricle and right auricle may be great and as a result the waist of the heart below the pulmonary artery segment may be widened; the right cardiac and supracardiac junctions may be elevated.

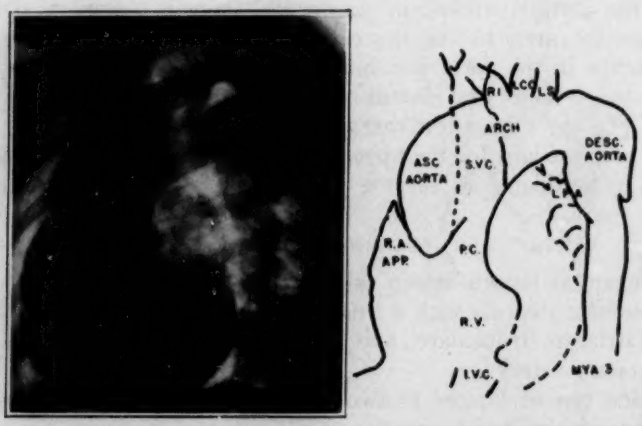

Fig. 6.—Tetralogy of Fallot in a girl aged 9 years. Angiocardiogram (left oblique) made two seconds after injection shows simultaneous visualization of right and left sides of the heart and of the aorta. The ascending aorta is dilated. The arch is deformed. The proximal portion of the aorta descendens is moderately dilated. The pulmonary artery is hypoplastic.

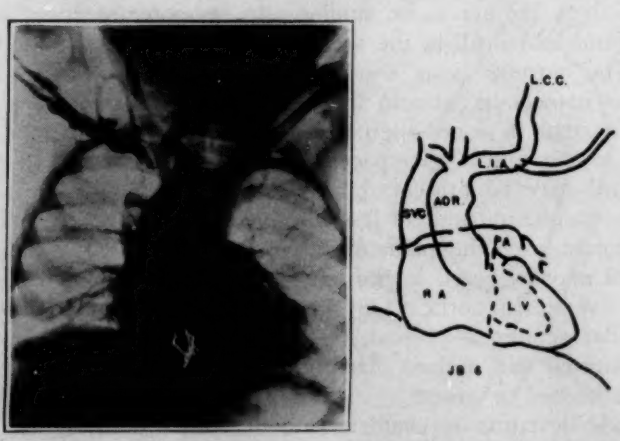

Fig. 7.—Tetralogy of Fallot in a girl aged 4 years. Angiocardiogram (posteroanterior) made three seconds after injection outlines the right and left sides of the heart and the aorta and pulmonary artery simultaneously. The pulmonary artery is small, and the conus is stenosed. The aortic arch is dextroposed. The aorta descendens passes downward to the right of the spine. The innominate artery is to the left of the spine.

Angiocardiography provides conclusive differentiation. In the tetralogy of Fallot the aorta and pulmonary artery are visualized simultaneously, usually within three seconds (fig. 6). The pulmonary artery may be so small as not to be identified. A shunt into the left ventricle may or may not be seen, depending presumably on how much blood passes through the interventricular septal defect.

The right ventricle and auricle are enlarged, but their cavities ordinarily are not greatly dilated. This is in contrast to isolated pulmonic stenosis, in which both cavities are greatly dilated. The pulmonary artery usually can be identified in the latter condition as a small vessel with an elongated narrowed segment between it and the large right ventricular cavity. Angiocardiography may be successful in demonstrating the associated anomalies which occur so commonly with the tetralogy. Coarctation of the aorta is seen with ease because of the concentration of diodrast in the aorta. In the same way, a right aortic arch, which occurs with some frequency, may be proved (fig. 7). Indeed, under no other circumstances is the aorta visualized as well by angiocardiography as in the presence of transposition of the great vessels.

2B. LEFT VENTRICULAR ENLARGEMENT

Many congenital lesions are associated with no other change in the cardiac configuration than that produced by hypertrophy and dilatation of the left ventricle. This change may be pronounced or may be so slight as to escape detection. The following conditions are included in this group: (*a*) coarctation of the aorta; (*b*) atypical coarctation of the aorta with absence of the left radial pulse; (*c*) aortic or subaortic stenosis; (*d*) patent ductus arteriosus without dilatation of the pulmonary artery; (*e*) "idiopathic" hypertrophy, and (*f*) isolated interventricular septal defect.

Physical Signs.—In coarctation, the heart may be within normal limits in size or may be slightly enlarged. Gross enlargement is apt to be associated with aortic insufficiency. The cardiac impulse is forceful. A systolic thrill may be present over the base of the heart, over the base of the neck and often over the vessels forming the collateral circulation. In the same way, a systolic murmur loudest at the base may be transmitted along the collateral vessels. Aortic insufficiency, if present, is associated with a diastolic murmur. On the other hand, murmurs may be lacking entirely. When recorded, the systolic murmur may be found to extend into early diastole and is maximum at or near the pulmonic area. This is due to the fact that the point of origin of the murmur, namely the narrowed segment of the aorta, is distant from the heart and the murmur is delayed as compared with the heart sounds. Hence the presence of systolic and early diastolic murmurs over the pulmonic area in a case of coarctation does not necessarily indicate that a patent ductus arteriosus also is present. Indeed, clinical proof of this additional condition is very difficult to elicit. The postmortem observation that left-sided collateral circulation is absent when the ductus is patent usually cannot be shown clinically.

In coarctation, the blood pressure, particularly the systolic, usually is raised. The blood pressure in the legs is diminished and may be lower than that in the arms, in contrast to the normal relationship. Enlarged tortuous vessels may be seen in the scapular area, in the intercostal spaces and in the course of the internal mammary arteries.

In the condition which we have described recently as atypical coarctation with absence of the left radial pulse, significant cardiac signs are lacking. The blood pressure in the right arm and that in the lower extremities are in normal relationship. It was elevated in 2 of our 3 cases. However, the pressure in the left arm is lower than that in the right.

The signs in aortic or subaortic stenosis are rather characteristic. The heart may or may not be enlarged. A systolic thrill may be felt over the entire precordium but is usually maximum or localized in the first and second spaces on the

right; it may be felt in the episternal notch. A loud, harsh systolic murmur occupying the whole of systole is maximum in the second space on the right (fig. 1 *E*). On the other hand, it may be heard anywhere on a line from this area to the apex and may therefore appear maximum to the left of the sternum at the third or fourth space. Characteristically, the murmur is transmitted along the great vessels and may be heard in the carotid and axillary vessels. The blood pressure may be normal or low, and the pulse pressure is reduced. In about one fourth of the cases a diastolic murmur also is present without other signs of aortic insufficiency.

The murmurs in patent ductus arteriosus already have been discussed in detail. Suffice it to repeat that a systolic murmur alone is rare except in infants. The pulse pressure is apt to be increased owing to a reduced diastolic pressure.

Idiopathic hypertrophy is rare beyond infancy unless associated with glycogen disease. There are no significant murmurs ordinarily. The heart is enlarged to the left.

Isolated interventricular septal defect also is a rare anomaly and often can be diagnosed only by exclusion. A very loud, rough systolic murmur heard best at the left sternal border in the third and fourth spaces is said to be characteristic. The murmur and an accompanying thrill may be heard, however, over the entire precordium. It extends throughout systole and may extend into diastole. In our case, the murmur was found to be composed of very high frequency components and was of high amplitude. However, this murmur is not characteristic. Indeed, our experience suggests that most of the conditions diagnosed as interventricular septal defect actually are aortic or subaortic stenosis.

The electrocardiogram is not helpful in differential diagnosis of this group of abnormalities. In most cases the electrocardiogram is within normal limits, or there may be a varying degree of left axis deviation. With any of the conditions in this group, any evidence of right axis deviation will suggest a patent ductus. Congenital heart block has been reported most often in connection with isolated interventricular septal defect.

Studies of the circulation are most important, if not pathognomonic. With coarctation of the aorta, pulse tracings made over radial and femoral pulses show a delay in the femoral pulse wave (fig. 8 *A*). This varies between 0.06 and 0.12 second, as compared with the normal pulsation, in which the femoral wave precedes the radial. Overactive pulsation can be recorded over the collateral vessels. There may be a palpable difference in temperature between the extremities, the hands being moist and warm while the legs and feet are cold.

In cases of atypical coarctation also, pulse tracings are very significant. The coarctation of the aorta is not sufficiently great to produce a delay in the femoral pulse. However, the left subclavian artery is partially or completely stenosed, and, as a result, the left radial pulse cannot be felt. When recorded, there is a noticeable delay before its peak is reached (fig. 8 *B* and 8 *C*). An anacrotic notch often is discovered over the left common carotid artery and sometimes over the innominate artery. These findings along with a normal relation of femoral and right radial pulses are pathognomonic.

Textbooks describe a small pulse pressure, an inactive aorta and a slow, delayed peripheral pulse as indicating aortic or subaortic stenosis. In our experience, a thrill (as described), a plateau type pulse and an anacrotic notch in the arterial pulse tracing taken preferably from the innominate artery seem to be more characteristic (fig. 8 *D*).

When a sizable shunt is present in patent ductus arteriosus, the circulatory dynamics are comparable to those of aortic insufficiency, namely an increased pulse pressure due to a drop in the diastolic pressure.

Conventional roentgen examination of the heart reveals in this group hypertrophy and dilatation of the left ventricle as shown by enlargement of the heart to the left and downward. However, this may be so slight as to be undetectable. Differentiating features are few. In some cases of coarctation the narrowed segment of the aorta just beyond the arch has been demonstrated by fluoroscopy. In a greater number indirect evidence of dilated intercostal arteries is afforded by notching of the under surface of the upper ribs, where the grooves for these vessels are situated.

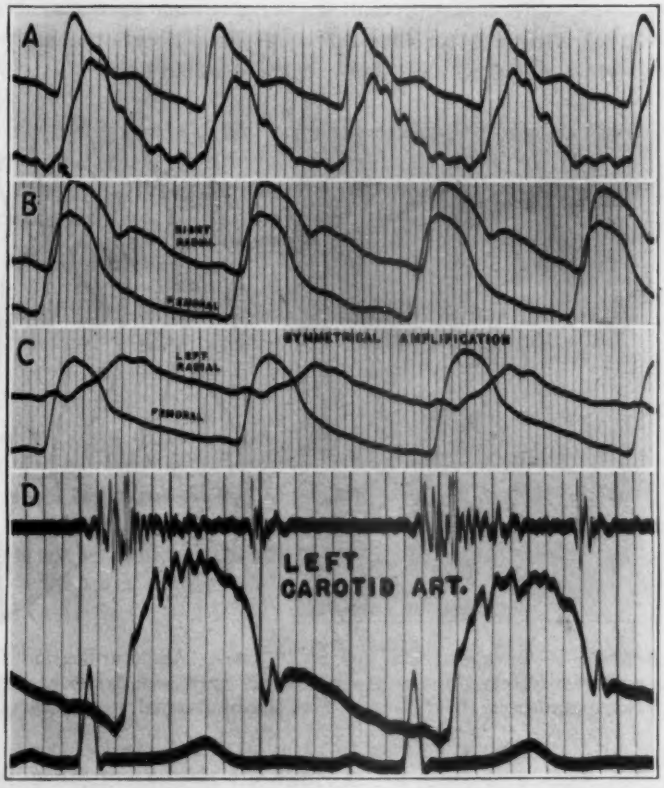

Fig. 8.—Pulse tracings in (*A*) coarctation of the aorta (the femoral pulse [lower] follows the left radial [upper]); (*B* and *C*) atypical coarctation (normal relation between the right radial and femoral pulses; the left radial pulse shows a slow rise and is of low amplitude) and (*D*) aortic stenosis (there are an anacrotic notch, systolic vibrations and a plateau).

In aortic stenosis the ascending aorta is described as small and its pulsation as quiet. However, this is not constant, since in several of our cases active pulsation was noted. Furthermore, dilatation of the ascending aorta is present sometimes and may be due to additional anomalies in the aorta, which are not infrequent.

Angiocardiography provides proof of the diagnosis of many of the conditions in this group. A long, narrowed, deformed aortic segment just beyond the arch has been demonstrated in all of our cases of coarctation (fig. 9). The dilated internal mammary arteries also are seen regularly.[10b]

Stenosis of the left subclavian artery can be shown, since this vessel normally is visualized regularly. In 1 of our cases the stump of the stenosed vessel was demonstrated. The arch of the aorta may be slightly narrowed and the descending portion is hypoplastic.[10e]

Aortic and subaortic stenosis presumably may be demonstrated directly, but our experience with this defect is limited. Additional anomalies, if present, are shown. The findings in patent ductus arteriosus have already been described in detail.

Our experience with isolated interventricular defect is limited to 1 case. In this case, a left to right ventricular shunt was indicated by continued opacification of the right ventricle beyond the time that it should have emptied. The fact that other anomalies which might account for the murmur were absent also was of aid. We have not used angiocardiography in cases of idiopathic hypertrophy, but the findings most likely would merely exclude other lesions.

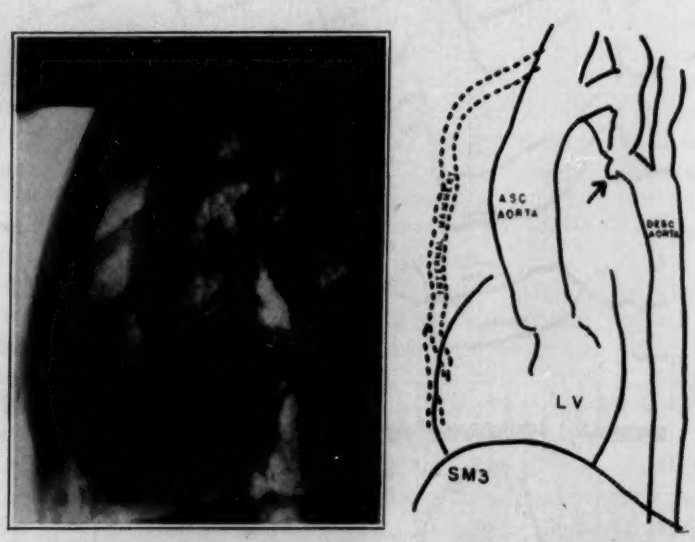

Fig. 9.—Coarctation of the aorta in a girl of 14 years. Angiocardiogram (left lateral) made seven seconds after injection shows a severely deformed and narrowed aortic isthmus. The coarcted segment measures about 6 cm. The dilated internal mammary artery is seen anteriorly.

3. RIGHT AORTIC ARCH

Persistence of the right aortic arch is a relatively frequent congenital lesion. It occurs in persons with an otherwise normal heart and circulation or in association with other congenital anomalies. Dysphagia may be the only clinical symptom, and this occurs only rarely. Since the presence of dysphagia and the roentgen appearance may easily lead to the diagnosis of mediastinal tumor, it is essential to be acquainted fully with the diagnostic criteria. Embryologically the condition results when the right branchial artery instead of the left develops into the aortic arch. The latter may be present in a rudimentary form as (1) a so-called dorsal diverticulum extending posterior to the esophagus and slightly to the left, (2) a rudimentary arch or ventral diverticulum, (3) a fully developed left aortic arch (double aorta), which is extremely rare or (4) a left innominate artery simulating an isolated transposed aorta. Unless simultaneous partial transposition of the viscera, including the diaphragm, is present, the descending aorta always passes through the diaphragm to the left of the spine.

The aorta may cross from the right to the left of the spine at one or two different levels, producing different roentgen findings as follows:

1. *So-Called High Crossing.*—The aorta is seen to ascend to the right of the spine, crossing to the left of the spine behind the esophagus, displacing the latter and the trachea anteriorly. The descending aorta is in its normal position. Roentgenologically, in the posteroanterior view the esophagus is found to be indented from the right instead of from the left, as normally found. In the right anterior oblique view the esophagus is indented from posteriorly at the level of the aortic arch.

Three variations may occur in this group:

(*a*) The left root may persist as a ventral diverticulum, visible to the left of the spine and easily identified by angiocardiography. The dorsal diverticulum does not change the roentgen appearance, since it causes an indentation similar to that of the "high crossing" of the aortic arch. It can be identified by angiocardiography.

(*b*) The right subclavian artery may originate as the last branch of the aortic arch and cross to the right, anterior to the esophagus. We have not observed this variety, but it has been reported occasionally as causing an indentation in the esophagus anteriorly above the level of the "high crossing" of the right aortic arch.

(*c*) The left fourth branchial artery may persist to form a left innominate artery. The right innominate artery is not developed, and the origins of the right subclavian and carotid arteries are separate. Actually, the appearance is that of an isolated transposition of the aorta. During life it can be identified only by angiocardiography.

2. *So-Called Low Crossing.*—The aortic arch and descending aorta are to the right of the spine, crossing to the left of the spine just above the diaphragm posterior to the esophagus to reach the normally located aortic opening of the diaphragm. As in group 1, the aorta indents the esophagus from the right in the posteroanterior view, while ordinarily there is a normal indentation of the esophagus in the right anterior oblique view. The same three variations previously described also occur here.

4. DEXTROCARDIA

For purposes of discussion, the following classification of dextrocardia has been proposed [98]:

Type I. Dextrocardia with complete or partial transposition of viscera (situs inversus): The relationship of the heart to the viscera is unaltered, resulting in a "mirror image" of the normal. The electrocardiographic pattern shows complete inversion. The electrical axis runs from left to right, being rotated 180 degrees from the normal.

Type II. Dextrocardia without transposition of viscera and with inversion of the cardiac chambers. The heart is transposed as in complete transposition, the left ventricle lying in front and the right behind. The electrocardiogram is of the "mirror image" variety.

Type III. Dextrocardia without transposition of the viscera and with normal arrangement of the cardiac chambers. The left ventricle lies anteriorly and the right posteriorly. The aortic arch presents on the left border, and the aorta descends to the left of the spine. The electrocardiographic pattern shows a normal electrical axis.

Type IV. Dextrocardia associated with congenital abnormalities of the thoracic cage, diaphragm or lungs. The arrangement of the chambers is normal, and the electrocardiographic pattern shows a normal electrical axis.

Type V. Acquired dextrocardia.

Types II and III usually require differentiation. Type II is rare and may be proved during life only by angiocardiography. Type III may be suspected during conventional fluoroscopic examination when on the patient's being turned into a slight left oblique position there results an exaggerated but otherwise normal configuration for this position.

SUMMARY

The common congenital lesions of the heart are discussed in the light of appearance of cyanosis, physical signs, circulatory dynamics and electrocardiographic and angiocardiographic findings. Careful application of the principles discussed usually permits precise diagnosis of the predominant lesions.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

RESISTANCE OF INFLUENZA VIRUS TO DRYING AND ITS DEMONSTRATION ON DUST. DERRICK G. F. EDWARD, Lancet **2**:664 (Nov. 29) 1941.

An experiment is described showing that after impregnation of a blanket with a suspension of influenza virus the virus survived drying under ordinary atmospheric conditions and could be distributed in the air on dust particles by shaking the blanket. The time for which the dried virus remained alive was estimated. There was little depreciation after three days; 10 per cent of the virus might persist for a week and 1 per cent for a fortnight.

LANGMANN, New York.

Metabolism; Infant Feeding; Milk and Other Foods

A COMPARISON BETWEEN DEHYDRATION FROM SALT LOSS AND FROM WATER DEPRIVATION. JOSEPH W. NADAL, SVEND PEDERSEN and WALTER G. MADDOCK, J. Clin. Investigation **20**:691 (Nov.) 1941.

In normal human subjects dehydration was produced by simple deprivation of water and by loss of sodium chloride. Loss of sodium chloride was brought about by constant jejunal drainage through a Miller-Abbott tube during four days without food preceded by a sixty day period of salt-poor diet. Data are presented to show that the two types of dehydration thus produced differ in the mechanism of production, in the manifestations and symptoms and in the treatment indicated.

Dehydration resulting from simple deprivation of water is characterized by thirst and oliguria, does not lead to impairment of the circulation and is completely relieved by the administration of water.

Dehydration resulting from abnormal loss of sodium chloride results mainly in a loss of extracellular fluid, a reduction in plasma volume and disturbances in the circulation. It is neither characterized by thirst nor relieved by the administration of salt-free fluids but is promptly relieved by fluid containing sodium chloride.

Observations on the energy, water, sodium and potassium balances during a period of total fasting and recovery suggested that during such dehydration and recovery the balances of sodium and potassium do not necessarily correspond to the water balance over short periods of time.

GUEST, Cincinnati.

THE ASSIMILATION OF FLUORINE BY RATS FROM NATURAL AND SYNTHETIC CRYOLITE AND FROM CRYOLITE-SPRAYED FRUITS. MARGARET LAWRENZ and H. H. MITCHELL, J. Nutrition **22**:451 (Nov.) 1941.

Lawrenz and Mitchell found that the fluorine of synthetic cryolite was more completely retained by rats than the fluorine of natural cryolite. "Weathering" of the fruit cryolite did not appreciably affect its assimilability and toxicity for the rats. This was not true for the synthetic cryolite, probably owing to its greater solubility.

FREDEEN, Kansas City, Mo.

THE UTILIZATION OF THE CALCIUM OF CAULIFLOWER AND BROCCOLI. MARGARET L. FINCKE, J. Nutrition **22**:477 (Nov.) 1941.

Fincke fed rats diets in which practically all of the calcium was derived from dried milk or in which half of the milk was replaced by dried broccoli or cauliflower to provide equivalent amounts of calcium. The availability of milk calcium was 87 per cent, of broccoli plus milk 79 per cent and of cauliflower plus milk 69 per cent. The combination of crude fiber and oxalate contents of the broccoli and cauliflower probably accounted for the total lowering of the calcium availability and utilization of these two diets.

FREDEEN, Kansas City, Mo.

DIETARY REQUIREMENTS FOR FERTILITY AND LACTATION. BARNETT SURE, J. Nutrition **22**:491 (Nov.) 1941.

Sure concludes from the results of this study that there is no definite proof that cystine is essential for lactation. He showed, however, that the lactation-promoting properties of a diet containing about 18 per cent casein were definitely improved by the addition of this amino acid.

FREDEEN, Kansas City, Mo.

Hygiene; Growth and Nutrition; Public Health

AN OCULAR POLICY FOR PUBLIC SCHOOLS. R. IRVINE, Am. J. Ophth. **24**:799 (July) 1941.

This comprehensive committee report on the examination of children's eyes in public schools and on problems pertaining thereto is taken up under the following headings: (1) methods of examination, (2) preventive measures, (3) reading problems and (4) care of patients unable to pay a private physician. W. S. REESE. [ARCH. OPHTH.]

HIGH STILLBIRTH AND NEONATAL MORTALITIES. DUGALD BAIRD and JOHN F. B. WYPER, Lancet **2**:657 (Nov. 29) 1941.

In the Aberdeen Maternity Hospital during the years 1938 to 1940, in 3,427 booked cases (contrasted with emergency cases) there were 187 stillbirths or neonatal deaths, a rate of 54.5 per thousand, as compared with 69.8 per thousand for the city as a whole. Of the full term babies (95) the cause of death was unknown for 25.3 per cent; trauma accounted for 18.9 per cent of the deaths, infection for 18.9 per cent and gross fetal deformity for 8.3 per cent.

Most of the premature babies (92) who died succumbed within twenty-four hours of birth because of feebleness. The cause of the premature onset of labor was unknown for 37 per cent; toxemia caused it in 15.2 per cent, debility in 13 per cent, twin pregnancy in 8.7 per cent, placenta praevia in 7.6 per cent, gross fetal deformity in 5.5 per cent and miscellaneous factors in 13 per cent.

The authors conclude that there is a large wastage of child life (approximately 80 per thousand births) associated with childbirth in Scotland, intimately connected with unfavorable economic conditions and malnutrition and fatigue in the mother. LANGMANN, New York.

Prematurity and Congenital Deformities

HISTOLOGIC EYE FINDINGS IN ARACHNODACTYLY. G. D. THEOBALD, Am. J. Ophth. **24**:1132 (Oct.) 1941.

The ocular measurements and microscopic observations in a case of arachnodactyly are reported, and the conclusion is drawn that two separate influences were responsible: First, after the fourth week an excitant caused the gigantic growth of the optic vesicle, with which the development of mesodermal tissues kept pace. Second, at the sixth month a depressant caused the arrest of development in both ectodermal and mesodermal tissues. The theories of arachnodactyly are briefly reviewed. W. S. REESE. [ARCH. OPHTH.]

THE PATHOLOGY OF THE PREMATURE INFANT. SIDNEY FARBER and EDITH L. POTTER, New York State J. Med. **41**:2047 (Oct. 15) 1941.

An abstract of this paper, which was read at a combined meeting of the New York Pathologic Society, the New York Academy of Medicine and the New York City Committee on Prematurity, is given. The importance of careful pathologic examinations is stressed. The pathologic examinations of premature infants should not be turned over to inexperienced pathologists but should be performed by those having experience and special interest in this field. Prematurity is not an acceptable cause of death. AIKMAN, Rochester, N. Y.

MORQUIO'S DISEASE. J. R. MARCOS and L. A. PIERONI, Arch. de pediat. d. Uruguay **12**:625 (Oct.) 1941.

The authors report 3 cases of this rare disorder which occurred in the same family. The children were aged 8, 9 and 10 years respectively. A fourth child, a girl, did not show the disease.

There was no consanguinity, and there were no hereditary disorders. Only 45 cases of this disorder have been reported in the literature to date.

These children did not show the hyperflaccidity of ligaments which is reported by other authors. On the contrary, all of these children showed limitation of articular movements and a tendency to polyarticular ankylosis. The authors consider this fact important, since it invalidates the hypothesis that a fundamental cause of deformity in this disorder is the flaccidity of the ligaments. These patients also showed a pronounced general hypoplasia of the trunk and of the extremities. All 3 of the children complained of pain and periodic cramps in the limbs. SCHLUTZ, Chicago.

PREMATURE DEATH RATE IN THE CLINIC AT BASLE. J. IMFELD, Ann. pædiat. **157**:47, 1941.

In recent years there has been an increased number of premature births in the hospital, which cannot be explained by an increased tendency to hospital nursing in these cases. Of 518 premature infants, 129 died (24.9 per cent). All deaths were counted, without any omissions. The mortality of the first ten days (early mortality) is 62 per cent of the total mortality. The death rate is highest in infants with the lowest birth weights and diminishes quickly with higher weights. In nursing the following points are of importance: the use of box beds, feeding with breast milk or breast milk combined with buttermilk for a long time; taking precautions against infections by masking all persons entering the nursery and by prohibiting visits of parents, and observing general principles of asepsis. Death was caused in half of the cases by debility, in about one third by pneumonia and in 11.6 per cent by cerebral lesions at birth. Debility and injury to the brain are the most important causes of the early mortality; pneumonia and alimentary disorders, of the subsequent deaths.

FROM THE AUTHOR'S SUMMARY.

THE ETIOLOGY OF DISTURBANCES OF DEVELOPMENT. GEORG LENART, Ann. pædiat. **157**:216, 1941.

In the genesis of malformation, as in the formation of physiologic features, gene content, cytoplasm and environment act together, although not in the same degree. This is not the case only in malformations differing among themselves, as in the same malformation a more genotypical or a more peristatic origin can predominate. Apart from the principal gene, in the genesis of hereditary malformations accessory genes (*Modifikationsgene*) and environment, in other words, the entire genotypical and peristatic milieu, play an important part. In certain cases they cause such a great variability of the gene manifestations, owing to alterations of the penetrability, of the activity of expression or of the specificity, that the very recognition of hereditary factors in the malformations in question can be endangered. In other cases, malformations due to environment can stimulate hereditary malformations. Without the knowledge and use of the results of experimental genetics, of genealogic statistics and of the twin method, no correct prognosis of heredity is possible. The practitioner should accordingly be extremely careful and reserved in giving eugenic advice.

AUTHOR'S SUMMARY.

Newborn

THE EFFECT OF DEPRIVING THE INFANT OF ITS PLACENTAL BLOOD. Q. B. DEMARSH, H. L. ALT, W. F. WINDLE and DAVID S. HILLIS, J. A. M. A. **116**:2568 (June 7) 1941.

Stimulated by consideration of the use of placental blood for transfusion purposes the authors studied the effect of immediate and delayed ligation of the umbilical cord on 50 babies. Studies of the blood (red cell count, hemoglobin content and number of reticulocytes) were done during the first week of life.

Significant changes were noted such as would result from depriving the infants of an average of 64 cc. of blood. Twenty-four per cent of the baby's blood is situated in the cord and placenta at birth. This amount of blood could raise the hemoglobin content of a 4 month old child by 3 Gm. per hundred cubic centimeters.

The authors are convinced that the cord should be ligated after separation of the placenta.

HEERSMA, Kalamazoo, Mich.

Acute Contagious Diseases

IMMUNIZATION AGAINST COMMON COMMUNICABLE DISEASES. FREDERICK H. MAURER, Illinois M. J. **80**:323 (Oct.) 1941.

Maurer presents a comprehensive discussion of present day prophylactic measures against common communicable diseases.

BARBOUR, Peoria, Ill.

THE KENNY TREATMENT OF INFANTILE PARALYSIS. WALLACE H. COLE and MILAND E. KNAPP, J. A. M. A. **116**:2577 (June 7) 1941.

There is presented a review of previous articles on this subject. The authors then present their observations on the results of treatment by Sister Kenny in 26 patients.

In principle the treatment involves avoidance of splinting, prevention and relief of muscle spasm with wet heat, reestablishment of normal nerve conduction and elimination of motor inhibitions.

Of 26 patients, 17 have recovered or are about well. The impression is that these patients have done better than under ordinary treatment and that no harm has followed the abandonment of immobilization.

HEERSMA, Kalamazoo, Mich.

THE THERAPY OF CEREBROSPINAL FEVER: A COMPARATIVE ANALYSIS OF THE THERAPEUTIC RESULTS IN 97 CASES FROM CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS. CARLO J. TRIPOLI and RICHARD E. SELSER, New Orleans M. & S. J. **94**:232 (Nov.) 1941.

The authors report the results of treating by various methods 97 patients proved to have cerebrospinal fever. From their experience they state: (1) that serotherapy, regardless of the type of serum used, does not compare in efficiency with either antitoxin or sulfanilamide; (2) that the combined use of antitoxin and sulfanilamide is more efficient than either alone; (3) that other sulfonamide compounds (sulfapyridine, sulfathiazole and sulfadiazine) are as efficacious as sulfanilamide, and (4) that the value of any type of intraspinal therapy is doubtful.

BERKLEY, Los Angeles.

POSTVACCINAL AND MEASLES ENCEPHALOMYELITIS. A. H. G. BURTON and J. H. WEIR, Lancet **2**:561 (Nov. 8) 1941.

A boy aged 6 months with postvaccinal encephalitis was treated with sulfapyridine plus intramuscular injections of blood from his father and from a recently vaccinated nurse.

A girl aged 6 years with encephalitis following measles was treated with sulfapyridine plus intramuscular inoculations of whole blood and convalescent measles serum.

Both recovered completely.

Since fatality rates in diseases vary considerably in different age groups and in different recorded series and spontaneous recovery does occur, the authors do not claim that the favorable therapeutic response was achieved by the agents employed, acting either singly or in combination. Nevertheless, in view of the extremely grave condition of the children, the first of whom was in an age group for which the fatality is high, the extensive involvement of the central nervous system and the rapid progression of the disease process without any evidence of amelioration until treatment was instituted, some encouragement is given for the future employment of the method.

LANGMANN, New York.

RECURRENT EXANTHEM IN THE COURSE OF SCARLET FEVER IN ONE THOUSAND CASES. J. M. LUSSER, Ann. pædiat. **157**:226, 1941.

In the 1,000 cases of scarlet fever in the Basle (Switzerland) Children's Hospital in the years from 1930 to May 1940 there were 368 relapses, 127 of them relapsing exanthems. The second and, at times, the third illness usually took a benign course. The periodic appearance concentrated in the third or fourth week. Children of 1½ to 15 years of age were affected, chiefly patients between 4 and 15 years; infants were thus less frequently affected.

The absolute frequency of relapses in hospital cases appears to have increased in the last few years and bears a relation to the proportion of beds occupied. The relative frequency shows only slight fluctuations. The increase in hospital beds for patients with scarlet fever corresponded to the increased number of patients admitted to the hospital with scarlet fever, whereby the desired improvement was again neutralized.

FROM THE AUTHOR'S SUMMARY.

Chronic Infectious Diseases

DENTAL STIGMAS OF CONGENITAL SYPHILIS. H. J. TEMPLETON, Am. J. Orthodontics **27**:531 (Oct.) 1941.

The malformations of the Hutchinson tooth and of the mulberry molar and the hypoplasia of the maxilla can be explained by the coincidence of intense syphilitic toxemia and the periods of embryologic development of these structures. Syphilitic dental dystrophies can be solved only by stamping out syphilis, by treating pregnant women or possibly by treating infants immediately after birth.

LEWIS, Dayton. [ANGLE ORTHODONTIST]

THE TRANSFER OF BISMUTH INTO THE FETAL CIRCULATION AFTER MATERNAL ADMINISTRATION OF SOBISMINOL. H. E. THOMPSON, L. T. STEADMAN and W. T. POMMERENKE, Am. J. Syph., Gonor. & Ven. Dis. **25**:725 (Nov.) 1941.

After oral administration of sobisminol mass there is a prompt appearance of bismuth in the maternal and fetal blood streams and in the placenta and umbilical cord. A spectro-

chemical procedure was developed to measure amounts of bismuth in small samples of biologic material.

"On the basis of the rapid transfer of bismuth to the fetal circulation after treatment with sobisminol mass, this drug might well receive consideration as a prenatal therapeutic preparation."

REUTER, Milwaukee. [ARCH. DERMAT. & SYPH.]

ROENTGENOGRAPHIC DIAGNOSIS OF CONGENITAL SYPHILIS IN UNERUPTED PERMANENT TEETH. BERNARD G. SARNAT, ISAAC SCHOUR and ROBERT HEUPEL, J. A. M. A. **116**:2745 (June 21) 1941.

Intraoral roentgenograms revealed evidence of congenital syphilis in a 4 year old Negro girl. This was present in the absence of changes in the long bones. Intraoral roentgenography should be added to the means of diagnosing and confirming the presence of congenital syphilis.

HEERSMA, Kalamazoo, Mich.

THE MANTOUX INTRADERMAL REACTION IN PRESCHOOL AND SCHOOL AGE CHILDREN IN VILLAHERMOSA. J. A. MANZUR, Rev. mex. de pediat. **11**:401 (Oct.) 1941.

It should be kept in mind as axiomatic that tuberculosis is the result of contagion. A tuberculous teacher with open tuberculosis sprays infected drops into the faces of the children day after day, and, as Italian authors say, these children receive a supertuberculization.

The Mantoux test was made on 1,256 children of both sexes in schools and homes.

Twenty-five per cent of the child population gave positive reactions; so it may be inferred that 25 per cent of the entire child population has tuberculosis. According to the last census Villahermosa has a population of 25,790, and as one third of it is formed by children from babyhood to 15 years there are in this city 8,596 children; according to the statistics, there are 2,149 children with tuberculous infection. And according to the calculation of Etienne Bernard that for every 4 cases of tuberculous infection there is 1 case of tuberculosis, there are 537 children ill with tuberculosis. The percentage of positive reactions was increased in the older children; more than one third of the older children gave a positive reaction. The percentage of positive reactions in boys 1 to 9 years of age is greater than that in girls of the same age. The percentage of positive reaction in girls and adolescents of 10 to 19 years is greater than that in boys of the same age. About 40 per cent of adolescent girls have a positive reaction. In the schools of Sons of Labor the percentage was high, as the children in these schools are poor and crowded together and have little food.

GIFFEN, Toledo, Ohio.

Diseases of Blood, Heart and Blood Vessels and Spleen

A GLOBULIN-FRACTION IN RABBIT'S PLASMA POSSESSING A STRONG CLOTTING PROPERTY. I. A. PARFENTJEV, Am. J. M. Sc. **202**:578 (Oct.) 1941.

A description is given of a globulin fraction isolated from rabbit plasma which possesses the property of clotting plasma.

It has been found that the toxicity of this fraction on intravenous injection is due to intravascular clotting.

Clotting globulin could be separated from that fraction of rabbit plasma which contains the major portion of the immune bodies.

HENSKE, Omaha.

THE THROMBIC ACTIVITY OF A GLOBULIN FRACTION DERIVED FROM RABBIT PLASMA. F. H. L. TAYLOR, EUGENE L. LOZNER and MARGARET A. ADAMS, Am. J. M. Sc. **202**:585 (Oct.) 1941.

The observation of Parfentjev that rabbit plasma contains a substance or physiologic activity capable of converting fibrinogen to fibrin is confirmed.

Parfentjev's material is apparently a pseudoglobulin which possesses true thrombic activity.

It may be differentiated from thromboplastin by its manner of preparation and its independence of calcium ion concentration in its action on fibrinogen.

Methods of preparing the material in a stable powdered form are presented.

HENSKE, Omaha.

THE USE OF RABBIT THROMBIN AS A LOCAL HEMOSTATIC. EUGENE L. LOZNER, HARRIET MACDONALD, MAXWELL FINLAND and F. H. L. TAYLOR, Am. J. M. Sc. **202**:593 (Oct.) 1941.

Observations are reported indicating that rabbit thrombin is of distinct value in the control of hemorrhage from small wounds induced by a standard trauma in normal persons and in 9 patients with and 2 without hemorrhagic diatheses bleeding spontaneously from small wounds.

The material apparently accomplishes its results by the instantaneous precipitation of fibrin. No toxic manifestations were observed following the application of rabbit thrombin to the small wounds.

It would appear desirable that these observations concerning the use of rabbit thrombin as a local hemostatic be extended.

HENSKE, Omaha.

AN IMPROVED METHOD FOR THE ESTIMATION OF QUANTITATIVE AND QUALITATIVE FACTORS. HEYWORTH N. SANFORD and ELEANOR I. LESLIE, J. Lab. & Clin. Med. **27**:255 (Nov.) 1941.

The authors describe a method for estimation of platelets in their own plasma. This method uses no anticoagulant until the cells are thrown down, and then heparin is used. The method requires apparatus at hand to keep the blood chilled throughout the procedure. This method also involves the use of platelet-containing plasma and platelet-free plasma in the coagulation times. The authors describe their findings with this method in several pathologic states.

GARD, Galveston, Texas.

THE INCIDENCE OF HEART DISEASE IN THE UNIVERSITY STUDENT AGE GROUP. MURIEL CUYKENDALL, New York State J. Med. **41**:2037 (Oct. 15) 1941.

This is a study of 6,489 men and women students at Cornell University during the academic year 1938-1939. At the student age, rheumatic diseases have already produced recognizable lesions in practically all susceptible hearts. Cardiac disease from syphilitic and degenerative diseases has not yet developed. All of these examinations were made by the author and consisted of careful physical examination and fluoroscopic examination. An electrocardiogram was usually made. Hypertension was diagnosed when the systolic blood pressure was above 140 and the diastolic pressure was above 90 mm. Hypertension was present in only 4.5 per cent of the men and 0.45 per cent of the women. Organic heart disease was found in 1.10 per cent of the men and 3.0 per cent of the women. The rheumatic type of cardiac disease was found in 82 per cent of these cases. The mitral valve was involved in 90 per cent of the rheumatic hearts. There was three times as much rheumatic heart disease among the women students as among the men. This is much greater than in any previously reported survey.

AIKMAN, Rochester, N. Y.

HEMOGLOBIN METABOLISM. M. C. G. ISRAELS, Lancet **2**:443 (Oct. 18) 1941.

Hemoglobin is formed by linking together a protein, globin, with an iron-containing pigment, "protohem." Protohem is a combination of ferrous iron with a substance, "protoporphyrin," which is closely allied to the pigments excreted in congenital porphyria.

There are four possible isomeric etioporphyrins, but the naturally occurring porphyrins all correspond to series I or series III. There is no simple chemical way whereby series I compounds can derive from series III or vice versa. The protoporphyrin of hemoglobin as well as that in reticulocytes belongs to series III.

Normal people excrete small amounts of coproporphyrin, about two thirds in the feces and one third in the urine, but all the fecal and at least half the urinary coproporphyrin is of series I and cannot therefore have been derived from the breakdown of hemoglobin. Coproporphyrin I is excreted in large amounts in hemolytic anemia and in the period of regeneration of blood after hemorrhage. In aplastic anemia, on the other hand, from one fifth to one tenth of the excreted coproporphyrin is of series III. Coproporphyrin III has also been found in poisoning by lead, sulfanilamide and other substances. Hence the excretion of coproporphyrin I seems to be linked with unusual erythropoietic activity, and that of coproporphyrin III, with depressed erythropoiesis.

"As Watson has said, what we need is a differential method permitting estimation of the amount of each isomer present without recourse to actual isolation. Until this happy day comes we must proceed, where we can, with the determination of the porphyrin isomers appearing in the various anemias so that there will be sufficient data free from the bias of individual cases."

LANGMANN, New York.

PATENCY OF THE DUCTUS ARTERIOSUS IN ADULTS. H. F. BETTINGER, M. J. Australia **2**:418 (Oct. 11) 1941.

The author disagrees with the general conclusions of Eppinger and Burwell that in patent ductus arteriosus blood is continuously shunted in large amounts (45 to 75 per cent of the blood pumped out from the left ventricle) from the aorta back through the ductus arteriosus into the pulmonary artery during systole as well as during diastole. Basing his statements on observa-

tions in a case in which death resulted from patent ductus arteriosus and on a number of statements in the literature, Bettinger concludes that:

1. In cases of uncomplicated patency of the duct the body attempts to establish a circulation as normal as possible. This is done by equalizing or approximation of the blood pressure in the aortic and the pulmonary system by means of a hypertrophy of the right ventricle and constriction of the medium and small arteries of the lungs. Shunt and overloading of the pulmonary system are thus kept at a minimum.

2. In the course of time the right ventricle will fail under this heavy task, shunt will occur and increase and enlargement of the left ventricle and excessive circulation through the lungs will result. Finally, the left ventricle will also fail, and life will terminate under the signs of general failure of the circulation. Eppinger and Burwell's conclusions remain valid, but only for the circumstances in which they were obtained, that is, for the period of decompensation.

GONCE JR., Madison, Wis.

MULTIPLE XANTHOMATOSIS TUBEROSA. M. ACUNA and A. PUGLISI, Arch. argent. de pediat. **16**:328 (Oct.) 1941.

The authors report a case of multiple xanthomatosis tuberosa, an extremely rare condition, in a boy 9 years old. Since the age of 5 years the child had had disseminated tumor masses distributed symmetrically around the neck, the upper part of both arms, the anterior and posterior surfaces of the thighs and both buttocks. The masses varied in size and were reddish yellow.

The liver was much enlarged. The tumor masses were of the type of lipoid granulomas such as are found in the Hand-Schüller-Christian syndrome.

There were no osseous changes. Various forms of treatment, including ultraviolet and roentgen therapy, were without effect.

SCHLUTZ, Chicago.

MYELOID CHLOROLEUKEMIA. A. CASTELLANOS and E. G. CONESA, Bol. Soc. cubana de pediat. **13**:309 (July) 1941.

The authors present a case of myeloid chloroleukemia in a Negro child 10 years old. The disorder developed in two separate stages. In the first stage the clinical picture was that of articular rheumatism. In the second stage the disease in a very few days presented an extremely grave picture, with the development of rapid anemia, hemorrhagic manifestations, high fever, prostration and very mild hepatosplenic enlargement.

In the second phase of the disorder one of the outstanding symptoms was a series of cutaneous and subcutaneous tumors. The largest ones were situated about the head and were of the size of a hazelnut, hard, firmly fixed in the skin, tender to touch and of a hemorrhagic tint. The entire body was also covered with similar lesions.

Biopsy of one of the tumors from the head and also the autopsy material from the liver and spleen showed the lesions to be involvements of myeloid leukemia. The blood picture was also characteristic of this disease.

SCHLUTZ, Chicago.

THE EFFECT OF SCHAUMANN'S DISEASE UPON THE HEART AND ITS MECHANISM. W. T. LONGCOPE and A. M. FISHER, Acta med. Scandinav. **108**:529, 1941.

In a series of 31 cases of sarcoidosis 6 patients showed some evidence of myocardial insufficiency during life or sarcoids of the heart and pericardium were discovered at autopsy. In 1 patient who showed no abnormalities of the heart during life a few lesions were found scattered through the myocardium at autopsy. The remaining 5 patients presented some evidence of the disease of the heart. Three of these patients died. Autopsies performed on 2 of them showed sarcoidosis of the myocardium and pericardium.

The 5 patients suffered from various degrees of heart failure, often with enlargement of the heart, arrhythmias and electrocardiographic changes.

KAJDI, Baltimore.

Diseases of Nose, Throat and Ear

ACUTE CATARRHAL MASTOIDITIS. CLAUDE C. CODY, Texas State J. Med. **37**:233 (July) 1941.

Cody reports 4 cases of acute catarrhal mastoiditis, which number he believes is sufficient to establish a clinical entity with a syndrome capable of being differentiated from other

otologic diseases, a distinctive roentgenogram, a characteristic pathologic picture at operation and a rational therapy.

The disease is a complication of acute catarrhal otitis media. The patient complains of a "stopped-up" or "stuffy" ear. The symptoms are impaired hearing and, later, tinnitus. There is no pain, fever or secretion in the middle ear.

In Cody's series, the patients were given the routine treatment for acute catarrhal otitis media but did not improve. Incision of the drum membrane was followed by a discharge of moderately thick, canary yellow fluid into the external canal. The discharge ceased after three or four days, with closure of the incision. Repeated incisions and various therapeutic measures failed to improve the condition. Tinnitus increased. There was no fever, no pain or headache about the ear or mastoid, no edema of the superior or posterior walls of the canal and no tenderness or edema over the mastoid. The blood count was normal. Roentgenograms of the mastoid region made more than thirty days after the onset of symptoms showed involvement of the entire mastoid bone but no breaking down of the cell walls.

The pathologic changes observed at operation were those of acute catarrhal inflammation. There was no evidence of bone absorption. The mucous membrane was thickened, and the cells were filled with a thin yellow secretion. The indications for operation were a persistent aural discharge, involvement of the mastoid, as shown by the roentgenogram, progressively increasing deafness of the obstructive type and tinnitus.

Cody states: "Simple mastoidectomy removes the pathologic condition, usually improves the hearing, relieves the tinnitus and probably prevents the later development of either chronic catarrhal otitis media or otosclerosis." SINGLETON, Dallas, Texas. [ARCH. OTOLARYNG.]

ROENTGEN THERAPY FOR CHRONIC INFECTIONS OF THE LYMPHOID RING OF WALDEYER. J. J. REBOIRAS, J. E. MOREAU and M. H. MOREAU, Arch. argent. de pediat. **16**:339 (Oct.) 1941.

The authors believe that roentgen treatment for hypertrophy and infection of the ring of Waldyer offers a painless therapeutic measure which is certain, efficacious and harmless. The use of roentgen therapy does not contraindicate later surgical intervention. Roentgen therapy can be begun with the child even younger than in the fourth year. Roentgen therapy is always indicated if surgical measures have been ineffectively used. SCHLUTZ, Chicago.

USE OF SULFONAMIDE COMPOUNDS IN OTORHINOLOGY. LUIS VAQUERO, Prensa méd. mex. **6**:143 (Oct. 15) 1941.

According to the observations and careful statistics of Bilchick and O'Kane, the number of surgical interventions for acute suppurative otitis media in children is not reduced by chemotherapy. If this treatment is insisted on and no attention is paid to the operative indications, the disease is retarded but does not improve. On the other hand, the purulent discharge diminishes notably, its duration being reduced 50 per cent compared with the control. In some cases the improvement is surprising, as suppurations which have lasted fifteen to twenty-five days may cease in twenty-four to forty-eight hours. If the operation has been insufficient and pus reappears beneath the mastoid scar, chemotherapy does not benefit and reintervention is indispensable.

Some authors think that sulfanilamide or one of its derivatives should be given routinely in every case of otitis media, but surgical operation on the membrana tympanica and on the mastoid may be used when indicated. Excessive confidence in chemotherapy, delays surgical treatment and may lead to disaster. GIFFEN, Toledo, Ohio.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

PROBABLE SPLENIC PORTAL THROMBOSIS WITH A ROENTGENOGRAPHIC STUDY OF ESOPHAGEAL VARICES. R. CIBILS AGUIRRE, M. BEKEI and J. R. CALCARAMI, Arch. argent. de pediat. **16**:3 (July) 1941.

The authors report a case of this condition in a child 9 years of age who had presented six different episodes of severe hematemesis from esophageal varices. Injection of epinephrine hydrochloride proved the splenic enlargement to be due to congestion.

The authors give a detailed report of extremely interesting roentgenologic findings in the case. By this method it is possible to demonstrate graphically the pathologic condition in the lower part of the esophagus. They discuss the various forms of splenic thrombosis and the treatment. Removal of the spleen and ligation of the coronary veins seem to offer the best results. SCHLUTZ, Chicago.

NICOTINIC ACID AND APHTHOUS STOMATITIS. J. DAMIANOVICH and R. RAVIZZOLI, Arch. argent. de pediat. **16**:21 (July) 1941.

The authors report on 15 patients with aphthous stomatitis, 11 of them children between the ages of 12 months and 6 years, who were treated with nicotinic acid given by the oral route. The dosage varied between 75 and 200 mg. in twenty-four hours and was divided in three or four doses. It was generally well tolerated. Only 1 patient showed marked capillary vasodilation after a total dose of 75 mg.

The effect was generally prompt, and complete cure was usually accomplished within three days.

Gingivitis is more resistant to the treatment. With this condition additional treatment in the form of topical astringents usually had to be employed. Abundant vitamin B complex was provided in the diet.

SCHLUTZ, Chicago.

Nervous Diseases

CHOKED DISCS IN LEAD ENCEPHALOPATHY. P. GOOD, Am. J. Ophth. **24**:794 (July) 1941.

Good reports 2 cases of lead poisoning in children, in 1 of which it was complicated by a tumor of the brain. He gives the following summary:

"1. Lead poisoning must be considered in children who show signs of increased intracranial pressure and choked discs.

"2. Roentgenographic density in the growth line of the long bones is a valuable aid in the diagnosis of lead poisoning.

"3. Drs. Buchanan and Bucey have shown in several cases that the severity of complications and the mortality of lead encephalopathy can be reduced by a decompression in addition to the approved medical treatment."

W. S. REESE. [ARCH. OPHTH.]

TREATMENT OF PNEUMOCOCCIC MENINGITIS. C. W. STEELE and J. GOTTLIEB, Arch. Int. Med. **68**:211 (Aug.) 1941.

Steele and Gottlieb present evidence which suggests that the abandonment of sulfanilamide and its derivatives in the treatment of pneumococcic meningitis may have been erroneous. They state that of 48 patients treated with sulfanilamide and its derivatives 68.75 per cent (33) recovered and 31.25 per cent (15) died, whereas of 67 similar patients treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) only 53.7 per cent (36) recovered and 46.2 per cent (31) died. If all patients who died during the first twenty-four hours are excluded, the respective percentages of recoveries become 71 and 62.7. Sulfapyridine was more effective than sulfanilamide and its derivatives for type III pneumococcic meningitis. Administration of type-specific antipneumococcus serum in conjunction with chemotherapy did not materially lower the mortality. As sulfanilamide is a safer drug, is more readily and uniformly absorbed and is as effective as or even more effective than sulfapyridine or sodium sulfapyridine for pneumococcic meningitis, its use should be continued until either of the other two drugs is shown to be superior.

J. A. M. A.

THE CEREBRAL PALSY PROBLEM. LYMAN C. DURYEA, New York State J. Med. **41**:1819 (Sept. 15) 1941.

This is one of three papers in a symposium on spastic paralysis. Cerebral palsy is the second greatest cause of crippling, and there are about 35,000 children with cerebral palsy in the United States. Special clinic and hospital facilities should be provided for these children, in order that new information may be obtained and also that the patients may receive better treatment.

A paper on "Neurologic Aspects of Spasticity and Athetosis" was presented by Tracy J. Putnam, and one on "The Differential Characteristics of Spasticity and Athetosis in Relation to Therapeutic Measures," by Winthrop Morgan Phelps.

AIKMAN, Rochester, N. Y.

VITAMINS E AND B_6 IN THE TREATMENT OF NEUROMUSCULAR DISEASES. L. M. EATON, H. W. WOLTMAN and H. R. BUTT, Proc. Staff Meet., Mayo Clin. **16**:523 (Aug. 13) 1941.

The authors report further results in the treatment of neuromuscular disorders with vitamins E and B_6. A previous report by Shelden, Woltman and Butt indicated no results in the treatment with vitamin E of 6 patients with amyotrophic lateral sclerosis, 4 with progressive muscular atrophy and 8 with progressive muscular dystrophy. The patients whose cases formed the basis of the previous report are included in the present series, having

received more prolonged and vigorous treatment, and, in addition, the authors report on an additional 5 patients with amyotrophic lateral sclerosis, 1 with progressive muscular atrophy and 1 with progressive muscular dystrophy, 1 with muscular atrophy of the Charcot-Marie-Tooth type and 1 with localized panatrophy. The total series consisted of 11 patients with amyotrophic lateral sclerosis, 5 with progressive muscular atrophy, 9 with progressive muscular dystrophy, 1 with muscular atrophy and 1 with localized panatrophy. The patients with amyotrophic lateral sclerosis were treated for periods ranging from six weeks to eleven and a half months. Those with progressive muscular atrophy were treated from four to ten months and those with muscular dystrophies from five and a half to nine months. The authors state: "At the time of completion of our study, no patient who had amyotrophic lateral sclerosis or progressive muscular atrophy was known definitely to have been benefited." Four patients who had muscular dystrophy wrote that they had improved, but examination of 2 of them revealed this improvement to be subjective only. The authors state finally: "We have found no conclusive evidence that vitamin E alone or in combination with B_6 or other vitamins is of benefit in amyotrophic lateral sclerosis, progressive muscular atrophy or progressive muscular dystrophy."

ALPERS, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

EXPERIMENTAL CEREBRAL CONCUSSION. D. DENNY-BROWN and W. RITCHIE RUSSELL, Brain **64**:93, 1941.

Cerebral concussion is a transient traumatic disturbance of the central nervous system which may lead to complete recovery or to death without detectable anatomic lesions. Denny-Brown and Russell studied this condition experimentally in animals subjected to head injury of known intensity produced by the measured blow of a hammer to the occipitoparietal area.

Whereas ordinarily loss of consciousness should be considered the criterion of concussion, in experiments with anesthetized animals this is not possible, and the criteria used were the following evidences of short-lasting but profound nervous disturbance: (1) loss of the corneal reflex; (2) loss of the pinna reflex; (3) marked change (rise) in blood pressure; (4) lasting inspiratory spasm, and (5) changes in muscle tone and reflexes.

In an experiment with an unanesthetized monkey these changes were observed to parallel the immediate, but transitory, unconsciousness usually called "concussion." In this "experimental concussion" there is interference with brain stem reflexes, lasting up to ninety seconds and terminating either in death or in recovery within five minutes. It is unaccompanied by any gross or microscopic intracranial lesion or by any significant change in intracranial pressure.

The blow required to produce this condition has a definite threshold. The object striking the freely suspended head must be traveling at a velocity of at least 25 feet (7.6 meters) per second. It is the sudden acceleration (or deceleration) of the head at about 48,000 feet (1.5 kilometers) per second per second which produces the injury. If the head is prevented from moving at the moment of injury, concussion could not be produced.

The effects of such a blow as seen in normal anesthetized monkeys may be summarized as follows: (1) loss of the pinna and corneal reflexes with movements of the vibrissae, indicating stimulation as well as paralysis; (2) immediate, sudden rise in blood pressure accompanied by peripheral vasoconstriction, indicating stimulation of the vasomotor center; (3) secondary, gradual fall in blood pressure, eventually leading to rapid vascular collapse and death, due to stimulation of the vagoglossopharyngeal reflex and the development of primary surgical shock unopposed by normal vasomotor reflexes; (4) sudden respiratory arrest due to stimulation of the respiratory center and loss of reflex respiratory activity, and (5) sudden flexor spasm of muscles, followed by diminished tendon jerks and abolition of the crossed extensor reflex.

Thus, in each instance, concussion is characterized by stimulation of the medullary centers, accompanied by reflex paralysis of these same structures. It is suggested that the same condition exists throughout the central nervous system.

A crushing injury of the head, with depressed fracture, produces a sudden rise in intracranial pressure. Regardless of the site of injury, this type of trauma produces damage to the medulla and upper cervical portion of the cord by plunging these structures through the foramen magnum.

The authors conclude that concussion is a generalized reversible "molecular reaction" induced by physical stress. It results first in excitation, later in excitation and reflex paralysis and finally in reflex paralysis alone. It is not secondary to contusion, which results from physical stress on the supporting vascular structures, nor is it due to increased intracranial pressure or to cerebral edema. MASLAND, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

CEREBRAL ELECTRICAL CHANGES IN EXPERIMENTAL CONCUSSION. DENIS WILLIAMS and D. DENNY-BROWN, Brain **64**:223, 1941.

The electroencephalogram of lightly anesthetized cats was recorded through dural leads during and after cerebral concussion produced by a hammer blow on the occiput.

Immediately after the injury, concomitant with the reflex paralysis which occurs, there is diminution or absence of electrical activity, affecting particularly the fast potentials. Abnormally slow waves, indistinguishable from those recorded in man, appeared at an inconstant interval (twenty-five to two hundred and five seconds) after the injury. In some instances they disappeared within ninety minutes; in others they persisted for long periods, depending on the severity of the injury. Similar changes were observed locally after a focal injury to the brain at the recording electrode.

The temporary diminution of electrical activity is associated with the general diminution in reflex activity occurring in cerebral concussion. The delayed development of slow waves may represent a stage in recovery from this condition.

MASLAND, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

A STUDY ON DISSOCIATION AND REORGANIZATION OF CEREBRAL FUNCTION. B. SCHLESINGER, Confinia neurol. **4**:14, 1941.

Schlesinger reports the case of a patient who had constructional apraxia, confined to the left upper extremity. She was unable to construct or draw simple patterns or to imitate postures with the left arm and hand. On the basis of this case study Schlesinger concludes that the activities of the parieto-occipital region are characterized by a high degree of dissociability. Lesions may result in loss of ability to carry out certain acts while other closely related performances remain intact. Various performances may be involved, in almost any combination, regardless of the time of acquisition and the degree of automatization.

Apart from the site and size of lesions which give rise to the phenomenon of selective elimination, dissociation may be due to the scattered arrangement of the nervous substrates which underlie the various performances, the varying functional characteristics of the involved areas, the presence of collateral innervation and individual variations in psychic organization.

If the lesion is not too extensive, disintegration of function in the parieto-occipital cortex is followed by reintegration, the structural basis for which are the equipotentiality and the collateral organization of the cortex.

DEJONG, Ann Arbor, Mich. [ARCH. NEUROL. & PSYCHIAT.]

OTITIC MENINGITIS: INDICATIONS FOR SURGICAL TREATMENT AND USE OF SULFONAMIDE COMPOUNDS. JUAN MANUEL TATO, An. de oto-rino-laring. d. Uruguay **11**:174, 1941.

Therapeusis of otitic meningitis is influenced by the following factors, among others: 1. The dynamics of inflammation, which concerns the onset, the evolution and other factors that may lead, on the one hand, to regression and cure or, on the other, to chronicity or fatality. 2. The type of lesion. A lesion which is primarily vasculosanguineous, exudative or proliferative or is particularly localized to the mucosa or the submucosa is easily reached by the drug in effective concentration. On the other hand, if the lesion is either a necrosing or a proliferating process in a closed cavity, the drug is of limited value. 3. The source of infection. The infection may originate from many different otitic areas and be carried by many routes. This fact necessarily influences the various types of therapy. Meningitis may occur (*a*) by direct spread, hematogenous, tympanic or labyrinthine, or (*b*) by indirect (or secondary) propagation from a sinus thrombus or a subdural or cerebral abscess. Or meningitis may be symptomatic and occur with any of the aforementioned conditions.

The author then reports in detail a series of 11 cases, with comments on each. In the first 6 cases treatment was with one of the sulfonamide drugs alone, while in the last 5 cases both surgical intervention and chemotherapy were required. There were 9 cures and 2 fatalities (a mortality rate of 18 per cent).

Tato concludes: 1. The drug should be given in sufficient dosage and preferably by mouth, but it may also be administered intraspinally. 2. The otitic focus should be eliminated except in cases in which the pathologic process is easily regressive and the progress of the patient is favorable. On the other hand, if the situation is doubtful, it is better to operate. The author refers again to the dynamics of inflammation in stressing the value of chemotherapy in cases in which there is ready approach (by the blood or the subarachnoid spaces) to the focus of infection.

Other measures in the treatment of this grave complication include serum therapy, lumbar and suboccipital puncture, blood transfusion and intravenous injection of dextrose and a hypertonic saline solution.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

HYPOPHYSIAL ADAMANTINOMA. C. C. LUGONES and A. A. FERRARIS, Arch. argent. de pediat. **16**:31 (July) 1941.

The authors report a case of this extremely rare condition in a child 12 years of age. Clinically the patient presented cranial hypertension, atrophy of the optic nerves, ballooned sella turcica with moderate calcifications, a hypothalamic syndrome, drowsiness and psychic changes. There were no endocrine changes.

At autopsy a tumor corresponding to the cranial pharyngioma was found. There was complete ossification of the pituitary portion. The rest of the tumor presented the appearance of a cholesteatoma, and some portions of it, the picture of a teratoma. The rare aspect of the case was the absence of any endocrine disturbances in spite of the fact that the entire sellar hypophysis was destroyed.

SCHLUTZ, Chicago.

PROBLEM OF HUMAN TRANSMISSION OF EQUINE ENCEPHALOMYELITIS. R. C. AGUIRRE, Arch. argent. de pediat. **16**:219 (Sept.) 1941.

The author is of the opinion that the possibility exists that a human being can become infected with the virus of equine encephalomyelitis but that this sort of infection is very remote. The diagnosis can be established by positive laboratory proof. The occurrence of the disease is rare, and all suspicious cases must be carefully studied. A mild epidemic of the disease appeared in the province of Córdoba, Argentina.

SCHLUTZ, Chicago.

PATHOLOGY AND TREATMENT OF OTOGENIC MENINGITIS IN CHILDHOOD. E. JENTS, Monatschr. f. Ohrenh. **75**:225 (May) 1941.

The author had opportunity to observe 8 children with otogenic meningitis, 6 of whom survived the disease. The ages ranged from 14 months to 10 years. In 6 patients the primary disease was scarlet fever or some other disease of childhood, in the course of which otitis developed, followed by meningitis. In 2 patients simple acute otitis was followed by meningitis. The meningitis developed in different stages of the otitis media, after four to thirty-one days. No other intracranial complication was observed in any instance. The diagnosis of otogenic meningitis is sometimes difficult to make when the child is suffering from some other disease which might simulate meningitic symptoms, such as scarlet fever or measles. Therefore early spinal puncture as a diagnostic means is advisable. Acute infection of the meninges produces polynucleosis, while in a later stage mononucleosis is present. This increased cell count, together with the clinical symptoms, is of great importance as an indication for operation. An average of the cell counts should be taken, as they vary with the sample of spinal fluid examined. In 5 cases the culture was found to be positive; in 4 instances Streptococcus pyogenes haemolyticus, and in 1 case Staphylococcus albus, was found. In both the fatal cases streptococci were present. It might be difficult to establish the picture of independent meningitis, but clinical symptoms, together with the proper changes in the spinal fluid, will support the diagnosis and indicate surgical intervention. It is essential to eliminate the focus of infection and to relieve intracranial pressure. Various operative methods can be employed. The author usually performed complete mastoidectomy, with exposure of the posterior and middle fossae. In addition, the connecting "bridge" is removed, a large exposure being thereby achieved. Jents refuses to perform an atticoantrotomy, as has been advised by Neumann, and is opposed to a radical mastoid operation. The second measure is necessary to combat the meningitis proper. This is carried out by reducing the increased pressure on the brain by means of daily spinal taps, with the removal of 30 to 80 cc. of fluid and the introduction of 20 to 30 cc. of air. Furthermore, chemotherapy in the form of azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate) and cylotropin (a preparation of methenamine and sodium salicylate) have been employed by the author. Azosulfamide was administered intrathecally and intramuscularly, as well as by mouth. The general resistance has to be built up and the heart supported. Repeated blood transfusions seem to be of great therapeutic value. The author feels that good results are achieved when these conditions are borne in mind and otitis media of childhood is not regarded as a minor ailment but the child is hospitalized in due time, so that early operation can be performed.

LEDERER, Chicago. [ARCH. OTOLARYNG.]

THE BIOLOGY AND PHYSICAL CHEMISTRY OF MONGOLISM. N. SCHACHTER, Ztschr. f. Kinderpsychiat. **8**:47 (July) 1941.

This paper reports a résumé of knowledge concerning the anatomy, physiology and biochemistry of mongolism.

JAHR, Omaha.

REEXAMINATION OF CHILDREN SUFFERING FROM CONVULSIONS. ODD MARVEL, Tidskr. f. d. norsk. lægeforening. **61**:63 (Jan. 15) 1941.

Of 63 children treated in 1923 to 1937 for convulsions, acute encephalitis, encephalopathy, vitium organicum cerebri or epilepsy 75 per cent were unimproved or dead; 15 per cent were free from convulsions but suffered from mental deficiency or were mentally normal but still displayed convulsions, and 10 per cent were healthy.

WALLGREN, Göteborg, Sweden.

Psychology and Psychiatry

THE TREATMENT OF CHILDHOOD SCHIZOPHRENIA BY METRAZOL SHOCK MODIFIED BY B-ERYTHROIDIN. FRANCES COTTINGTON, Am. J. Psychiat. **90**:397 (Nov.) 1941.

A total of one hundred and fifty-five treatments were given to 10 patients. Five boys had over twenty treatments each; 3 had nine, and 2, seven. Beta erythroidine is a curare-like substance administered for prevention of fractures during convulsive therapy. The physiologic effects of the drug are discussed and the method of procedure described. Eight of the 9 children with schizophrenia treated, including 2 previously treated by unmodified shock, showed improvement with metrazol therapy. Nine of the 10 had no fractures. The tenth sustained a fracture through a delayed unmodified seizure.

JAHR, Omaha.

A PSYCHOANALYTIC STUDY OF A FRATERNAL TWIN. DOUGLASS W. ORR, Psychoanalyt. Quart. **10**:284, 1941.

Orr presents data from the analysis of a fraternal twin of middle age who showed acute maladjustments and addiction to alcohol and drugs. In childhood he had been a good, conforming child, in contrast to his brother, who had temper tantrums. His psychic conflicts were as follows: 1. He tried to be like his twin because if he excelled his twin he felt anxious lest the latter be hostile. If his twin excelled him he felt hostile and was anxious because of his hostility. 2. He tried to obtain love and approval from his parents by trying at one time to be like his twin and at others to be entirely different from him. This secondary conflict was the result of his struggle between being an individual (with an individual ego) and being a twin (his ego being fused with that of his twin) and his struggle between his unique inherited potentialities and an environment that accentuated the similarities between the twins. Orr believes that these conflicts could have been avoided if the parents had minimized the similarities and emphasized the differences between the two boys.

PEARSON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

Diseases of the Genitourinary Tract

THE RELATION OF HIGH AND LOW UREA CLEARANCES TO THE INULIN AND CREATININE CLEARANCES IN CHILDREN WITH THE NEPHROTIC SYNDROME. KENDALL EMERSON JR., PALMER H. FUTCHER and LEE E. FARR, J. Clin. Investigation **20**:361 (July) 1941.

In a group of 33 nephrotic children less than 10 years of age, the urea clearance was abnormally high in 14 patients. The persistent high clearance, commonly 150 to 200 per cent and in 1 patient between 200 and 300 per cent, was interpreted as a manifestation of generally increased renal excretory activity, since the inulin and creatinine clearances were also elevated above normal to approximately the same degree. Insofar as tubular activity could be estimated from the ratio of exogenous creatinine clearance to inulin clearance, it appeared that this activity was as much accelerated as the glomerular filtration.

GUEST, Cincinnati.

ON THE ALLERGIC PATHOGENESIS OF ACUTE NEPHRITIS. M. CH. EHRSTRÖM, Nord. med. (Finska läk.-sällsk. handl.) **9**:204 (Jan. 18) 1941.

Ehrström presents short case histories of acute nephritis developing in connection with various kinds of allergic manifestations, food allergy, asthma, erythema nodosum, polyarthritis and rheumatic fever. This relation speaks in favor of an allergic genesis of the nephritis.

WALLGREN, Göteborg, Sweden.

Diseases of the Muscles, Bones, Joints and Lymph Glands

MARBLE BONES AND OPTIC ATROPHY. R. O. RISER, Am. J. Ophth. **24**:874 (Aug.) 1941.

Riser gives a short history of Albers-Schönberg disease and reports a case, commenting that his is the first discussion of the disease from an ophthalmologic viewpoint. He gives the following summary:

"1. Optic atrophy and associated ocular findings are very commonly found in infants and children with osteopetrosis.

"2. Optic atrophy is not a feature of adult osteosclerosis.

"3. An ophthalmologist, confronted by a young patient with optic atrophy and negative Wassermann test, may well advise roentgenological studies of the child's bones, for he might be dealing with a case of Albers-Schönberg's disease." W. S. REESE. [ARCH. OPHTH.]

AUTOPSY IN A CASE OF DYSTONIA MUSCULORUM DEFORMANS. J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **6**:87 (June) 1941.

Nielsen reports the case of a white boy of German descent who was normal until the age of 18 months, when there was an episode of torsion of the spine during a "cold." Thereafter he walked somewhat on his toes, a difficulty which increased, so that at 12 years of age he was considered "spastic" and had begun to have torsion of his arms. An attack of influenza when he was 16 was followed by renewed torsion of the spine and flexion contractures of the legs, which prevented his ever walking again. At the age of 25 he was confined to bed with extreme lordosis and torsion, as well as marked flexion contractures of all the extremities. Passive straightening was possible in the upper extremities and partially so in the lower. He could chew and swallow but not articulate. There were no athetoid movements. The sphincters remained under control. He died at the age of 32, of pneumonia and pneumococcic meningitis. The clinical diagnosis was dystonia musculorum deformans. At autopsy the essential pathologic changes were progressive degeneration of the nerve cells, particularly in the putamen and the dentate nucleus. In the thalamus less marked cellular changes with status marmoratus were observed. Nielsen considers the condition to have been a system disease because of the bilateral involvement of the dentate nucleus and the putamen.

MACKAY, Chicago. [ARCH. NEUROL. & PSYCHIAT.]

MULTIPLE MYELOMAS IN A CHILD OF EIGHT YEARS. J. C. BERTRAND, D. FUKS and A. B. AYROLO, Arch. argent. de pediat. **16**:147 (Aug.) 1941.

The authors report this very rare condition in a child of 8 years. Multiple proliferative foci were found in the long and in the flat bones. There were also pronounced spinal and other neurologic symptoms. The bones of the head and spine showed no demonstrable lesions on the roentgenogram.

Biopsy of the tumor mass from the medullary portions to the long bones and sternal puncture showed it to be a myelosarcoma with marked dissemination of multiple myelomas throughout the osseous system. The condition terminated fatally. SCHLUTZ, Chicago.

Diseases of the Eye

RETINAL TUBEROUS SCLEROSIS (BOURNEVILLE'S DISEASE). A. LOEWENSTEIN and J. STEEL, Am. J. Ophth. **24**:731 (July) 1941.

Loewenstein and Steel give the following summary:

"The case described was observed in a boy of 3½ years, with no history of hereditary defect. He had epileptic fits, but presented no sebaceous adenomata. Ophthalmoscopic examination showed gray-green tumors, exudative retinitis, retinitis proliferans and angiomatous nodules. Upon subsequent examination, the picture changed. Anatomical examination of the other eye showed multiple tumors with nerve fibers and regular layers straight as an arrow —neural cells producing closed and open cysts, a thickened membrana limitans interna, pyramidal tumor of the disc, and lack of the bacillary layer. Also present was a typical choroidal angioma and angiomatous growth at the retinal surface

"We assume that the round nucleated tumor cells arise from the round cells of the inner wall of the optic cup which normally would have developed into ganglion cells—they grow in single layers and produce cysts. A mechanical explanation of the genesis of cysts is given.

"The condition is a *primary ectodermal* malformation and the disturbance of balance of ectoderm and mesoderm leads *secondarily* to a *mesoderm* tumor. The opposite sequence occurs in Hippel-Lindau's disease, the *primary* growth being *mesodermal* and the *secondary ectodermal.*

"All four of the phacomatoses arise from congenital, usually hereditary malformations, in which certain undifferentiated cells start to grow and bring disorder into the germinal layers by disturbing the mutual pressure of the tissue (Gurvič) needed for a normal development. The drive of growth is assumed to be a chemical one—parallel to the carcinogenic substances, a surplus of which produces a growing tumor. A defect causes the different kinds of regressive metamorphoses known as familial degenerations of cerebrum, retina, cornea, and other tissues."

W. S. Reese. [Arch. Ophth.]

Gonorrheal Ophthalmia and Gonorrheal Ophthalmia Neonatorum. E. B. Muir, Am. J. Ophth. **24**:879 (Aug.) 1941.

Muir reviews the forms of treatment of gonorrheal conjunctivitis, citing various authorities. He bases the following conclusions on the records of 115 cases of gonorrheal ophthalmia and of 126 cases of gonorrheal ophthalmia neonatorum:

"Progress in the treatment of gonorrheal eye disease may be said to have made three considerable advances in the last decade. In the order of their introduction, credit for these advances must be given to: 1. Non-specific or foreign-protein therapy. 2. Artificial-fever therapy. 3. Sulfanilamide therapy. The second is closely allied to the first in its rationale. The third achieves its results in an entirely different manner and is a form of chemotherapy. In none of them is the mode of action entirely understood, and their use is fundamentally empirical. All three have reduced the length of hospitalization; all have diminished the frequency and severity of corneal complications.

"While sulfanilamide has produced more brilliant results than any previous therapeutic measure, it must be used with caution and a full understanding of its potential dangers. There will continue to be cases of gonorrheal conjunctivitis, resistant to sulfanilamide, in which recourse to all available therapeutic resources will be necessary to prevent loss of the eyes.

"The methods and procedure used by the old masters of ophthalmology must not be discarded. When properly and skilfully used, they will continue to be found of value in many cases of gonorrheal eye disease."

W. S. Reese. [Arch. Ophth.]

Keratoconjunctival Lesions Observed at High Altitudes in Bolivia. A. Solares, Am. J. Ophth. **24**:900 (Aug.) 1941.

Solares describes a condition affecting adolescent boys, usually under 15 years of age, in the high altitudes of Bolivia. They have red eyes and contracted palpebral fissures, the redness being predominantly at the limbus, either surrounding the cornea or of double semilunar configuration, the central part extending to the ends of the horizontal diameter. The color is light red, livid or violet, and in some instances the coloration is made up of fine blood vessels. There are juxtalimbal neoformations which rise above the surface of the eyeball, grayish white, with a gelatinous aspect similar to that found in vernal conjunctivitis. Solares describes this disease fully and compares it to vernal catarrh. He believes that it is a separate disease entity and designates it exuberant perikeratoconjunctivitis.

W. S. Reese. [Arch. Ophth.]

Bitot's Spots in Trinidad. V. M. Metivier, Am. J. Ophth. **24**:1029 (Sept.) 1941.

Metivier discusses Bitot's spots in relation to xerophthalmia and their occurrence in Trinidad. He concludes that a simple method of assessing the state of nutrition among large groups of children is the incidence of angular stomatitis, phrynoderma and Bitot's spots.

W. S. Reese. [Arch. Ophth.]

Aplasia of the Optic Nerve. Harold G. Scheie and Francis Heed Adler, Arch. Ophth. **26**:61 (July) 1941.

Aplasia of the optic nerve is a congenital anomaly rarely seen except in grossly malformed eyes. In fact, Cords (Einseitige Kleinheit der Papille, *Klin. Monatsbl. f. Augenh.* **71**:414-418, 1923) stated that it was one of the rarest of congenital malformations.

Aplasia of the optic nerve may occur from two sources, because the optic nerve arises from mesoderm and from neural ectoderm. The paraxial mesoderm first grows into the fetal fissure, laying down the hyaloid vessels and connective tissue. The fetal fissure then closes from the rim of the optic cup to the hyaloid vessels, the site of the future optic papilla. If the mesoderm fails to enter the fissure complete closure may occur, preventing subsequent growth of nerve fibers into the optic stalk after they develop from the ganglion cell layer of the retina.

This results in true aplasia, or complete absence of the optic nerve, not even the central vessels being present.

If development has proceeded normally except for failure of development of the ganglion cell layer of the retina, the optic nerve head, though small because of the absence of nerve fibers, should be present, as evidenced by the central vessels. Such an optic nerve head is seen clinically in well developed eyes, and in the case reported the condition was bilateral. The condition must be differentiated from atrophy of the optic nerve.

SPAETH, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

FUNCTIONAL STRABISMUS. R. ARGAÑARAZ, Arch. de oftal. de Buenos Aires **16**:409 (Aug.) 1941.

Argañaraz defines functional strabismus as a disease of the sensorimotor apparatus of vision characterized by a deviation of the visual axes. A disturbance of the motor function constitutes its initial symptom.

After describing in detail his views concerning normal binocular vision, the author states the opinion that the lesion in functional strabismus is toxic-infectious, is transitory or permanent and is sudden in onset, appearing usually before the age of 3 years during convalescence from some infectious disease of childhood (measles, whooping cough, smallpox or gastrointestinal intoxication). The lesion, located either in the reflex motor center in the pons or in the cortical voluntary center, gives rise to a spasm of convergence, which if permanent is followed after some years by contracture and ankylosis of the tissues and aponeuroses over the internal portion of both globes.

The relation between accommodation and convergence in cases of a preexisting hypermetropia favors the occurrence of the spasm, acting, however, as an adjunct and not as a causative agent, as maintained by Donders. The presence of excessive hypermetropia, astigmatism and anisometropia in the squinting eye the author attributes to a persistence in it of fetal anatomic and physiologic characteristics, with often an amblyopia not accounted for by any coexisting ophthalmoscopic lesion.

Argañaraz considers the explanation that the squint is a congenital defect or the result of nonuse as erroneous; he considers it a sensorial hemiplegia with amblyopia or lack of vision in one eye. He likewise considers the explanation of the lack of diplopia in squint as the product of a psychic or cerebral suppression of the image of the squinting eye as another current mistake, the condition being due to an early interruption of the development of binocular vision.

Squint usually appears during the second and third years and often in the first; the earlier the onset, the worse the prognosis. When it occurs in the fourth or fifth year, the prognosis is better, owing to the development by that time of some degree of binocular vision and fusion. The deviation is apt to lessen and occasionally disappear in late infancy or childhood, and after 20 it is usually permanent.

In some cases there seems to be a familial predisposition.

Argañaraz does not accept Worth's explanation that the essential cause of strabismus is a defect in the fusion faculty. He considers the amblyopia the result and not the cause of the primitive deviation of the ocular axes.

Deviation of the eyes from other causes (corneal opacities, cataract, choroiditis, etc.) has no relation to functional squint. This is rarely cured by the ophthalmologist; in 6 to 9 per cent of cases parallelism is reestablished spontaneously; in 90 per cent the sensorimotor lesion is incurable.

The ocular defect is of first consideration. The prescription of glasses should be preceded by complete paralysis of accommodation for a week followed by full correction and constant use of the glasses. Good results may be obtained in 8 to 10 per cent of the cases in which amblyopia and the disturbance of fusion are not pronounced.

The orthoptic treatment is the most scientific and rational, but its results in practice are poor, owing possibly to lack of patience and constancy. Its objective is to combat the amblyopia and favor the development of binocular vision and fusion by stereoscopic exercises. It should be commenced as early as possible. Of the different means employed, Argañaraz prefers Maddox's cheiroscope. Occlusion of the good eye for certain periods is an essential adjunct to this treatment.

Operative treatment for the correction of the deviation should not be undertaken until after the eighteenth or twentieth year. All surgical procedures give good results if indicated and properly executed. The author discusses in detail simple tenotomy, double tenotomy, tenotomy with advancement and double advancement. C. E. FINLAY. [ARCH. OPHTH.]

DIKTYOMA OF THE CILIARY BODY. I. CZUKRÁSZ, Arch. f. Ophth. **142**:619, 1941.

The blind left eye of a boy 3 years of age was removed because of inflammation and a yellow reflex from the fundus suggesting glioma. Histologic examination revealed a diktyoma (Fuchs), a neoplasm arising from the unpigmented epithelium of the ciliary body and resembling embryonic retina. The author considers the tumor to be benign, which is contrary to the opinion of Fuchs and others. An incomplete review of the literature is given.

P. C. KRONFELD. [ARCH. OPHTH.]

HEREDITARY PTOSIS AND IMBECILITY. J. TATÁR and Z. VON PAP, Arch. f. Ophth. **142**:627, 1941.

This report concerns a Hungarian family in which the father, 4 sons and 2 daughters showed the following anomalies: bilateral ptosis, blepharophimosis, underdevelopment of the tarsi, paralysis of the superior rectus muscles and overdevelopment of the eyebrows. One son was an imbecile.

P. C. KRONFELD. [ARCH. OPHTH.]

GENUINE TETANIC NUTRITIONAL CATARACT. G. BIETTI, Klin. Monatsbl. f. Augenh. **105**:299 (Sept.) 1940.

The author refers to the divers forms of nutritional cataract, described by a number of writers and compiled by Jess, and reports on his research with different types of nutrition in rats. The cataract produced was identical with the spontaneous cataract observed in rats. It developed in 80 to 90 per cent of 120 rats. Tables and photomicrographs serve as illustrations.

Bietti concludes that long-lasting and latent nutritional tetany accompanied by cataract may be produced independently of rickets by means of a diet poor in calcium as compared with phosphorus and lacking calcium-fixing vitamin D. The diet should contain calcium and phosphorus in a ratio of not more than 1 : 4, with a calcium level not exceeding 0.040 per cent. In rachitic animals even a smaller disturbance of the calcium and phosphorus ratio will produce cataract, although it does not occur so constantly. An increased phosphorus content in the diet will further to some extent the formation of cataract, which is accompanied by increased neuromuscular irritability and distinct hypocalcemia. The artificial cataract he produced represents a new type, namely a purely tetanic nutritional form, independent from rickets. The experiments, in Bietti's opinion, are a contribution to the etiology of nutritional cataracts, and in addition the simplicity and reliability of the method of research make it readily adapted to experiments on opacification of lens fibers and on cataract in general. The difficulty of experimenting with the small eyes of rats may in due time be overcome through use of larger animals.

K. L. STOLL. [ARCH. OPHTH.]

Skin Diseases; Allergy

STEVENS-JOHNSON DISEASE WITH COMPLETE VISUAL RECOVERY. ISADORE GIVNER and HARRY AGELOFF, New York State J. Med. **41**:1762 (Sept. 1) 1941.

This condition, closely related to erythema multiforme exudativum, shows, in addition to involvement of the skin and mucous membranes, extensive involvement of the eyes, such as purulent conjunctivitis, suppurative keratitis, corneal ulceration, purulent ophthalmia and even total blindness.

A case is reported in a child 4 years of age. She made a good recovery after treatment with azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate) together with applications of boric acid and metaphen in a dilution of 1 : 2,500. Givner and Ageloff believe that sulfathiazole will give even better results.

AIKMAN, Rochester, N. Y.

RECKLINGHAUSEN'S DISEASE IN A CHILD THREE AND ONE-HALF YEARS OLD. T. VALLEDOR, L. EXPOSITO, A. DE FERIA and A. S. NODARSE, Bol. Soc. cubana de pediat. **13**:357 (Aug.) 1941.

When the patient was 8 months old, a small tumor mass appeared at the external angle of the left upper eyelid. This showed slow and progressive enlargement. At the same time numerous small areas of pigmentation appeared in various parts of the body. A marked kyphoscoliosis of the spine developed and was mistaken for Pott's disease. Biopsy of the tumor mass in the upper lid showed neurofibromatosis.

SCHLUTZ, Chicago.

DERMATITIS VENENATA PROVOKED BY COLEOPTERA GENUS PAEDERUS. PEDRO L. BALIÑA, Rev. argent. de dermatosif. **23**:522, 1939.

In 1915 the author described a dermatitis due to an insect. Later investigations of Baccaredda in Italy and Dallas in Argentina have identified Paederus fuscipes as the cause of this dermatitis. The condition is frequent in the summer. It begins twenty-four to forty-eight hours after the contact of the insect with the skin. First there is an intense pruritus. Later vesiculation appears. The eruption is self limited and disappears in five to eight days except when secondarily infected. The dermatitis is produced by the crushing of the insect against the skin. A yellow fluid is thus liberated, which stains the skin and produces a burning sensation. This substance if carried to the eyes with the fingers may produce conjunctivitis. The patch of dermatitis is usually 2 to 3 inches (5 to 7.5 cm.) in diameter, and in some instances a linear lesion was noticed, simulating herpes zoster or dermatitis venenata due to plants. The latter type of lesion was probably due to unconsciously rubbing the insect against the skin. The eruption is located usually on uncovered parts of the body, face, neck and hands. Paederus is found in some regions of Argentina, Brazil and Ecuador.

CAÑIZARES, New York. [ARCH. DERMAT. & SYPH.]

Teeth and Dentistry

THE INFLUENCE OF THE FORMATIVE DENTAL ORGANS ON THE GROWTH OF THE BONES OF THE FACE. LAWRENCE W. BAKER, Am. J. Orthodontics **27**:489 (Sept.) 1941.

According to Baker, growth energy is stored within the formative organs of the teeth and this energy is responsible for the rapid growth of the facial bones during childhood and adolescence. Experiments conducted on rats, cats, and pigs by the removal of some of the formative organs (rats, incisors; cats and pigs, permanent teeth) disclose that there is an arrest in the growth of the facial bones on the side of the operation and in the direction in which the experimented-on teeth would grow. The author regards forming teeth in animals and human beings, both temporary and permanent, as highly specialized epiphyses which act against the pressure of the growing bones of the skull.

LEWIS, Dayton. [ANGLE ORTHODONTIST]

STUDIES ON THE PRINCIPLES OF SKELETAL GROWTH: I. THE TEETH. I. SCHOUR, Am. J. Phys. Anthropol. (supp.) **28**:13 (Sept. 30) 1941.

Each stage in the development of a tooth is governed by definite principles or laws, the integration of which makes for orderliness in the elaboration of its form, size and function. The development is a continuous lifelong process, which consists of:

A. Growth:

1. Initiation of proliferative activity at predetermined sites on the dental lamina.

2. Proliferation of the tooth germ, with changes in the form and size of the enamel organ.

3. Histodifferentiation of the formative cells, which give up their proliferative capacity and acquire their appositional growth potential. The law of inverse relationship between proliferation and differentiation is well illustrated in the developing tooth.

4. Morphodifferentiation. The morphologic pattern (form and relative size of the tooth) is well established by the outlining of the dentinoenamel junction by the formative cells.

5. Apposition of enamel and dentin matrix proceeds according to a definite pattern. The appositional growth potential is expressed at a definite rate and chronologic scheme. The formative cells begin their work at definite times and at definite sites (growth centers) on the dentinoenamel junction. The rates obey the law of growth gradients (age, locus and anteroposterior direction). The resultant incremental growth pattern consists of a series of gnomonic curves whose form is determined by the dentinoenamel junction.

B. Calcification of deposited matrix.

C. Eruption of the tooth, continuous throughout life.

D. Attrition or functional wear of the tooth.

[ANGLE ORTHODONTIST.]

Miscellaneous

TOXIC REACTION TO SULFAPYRIDINE. A. ALLEN GOLDBLOOM, LOUIS GREENWALD and H. REINSTEIN, J. Lab. & Clin. Med. **27**:139 (Nov.) 1941.

Three cases of toxic reactions to sulfapyridine (in adults) are reported. There were varying degrees of leukemoid blood picture. There was also an acute hemolytic anemia in

each case, and a secondary thrombopenic purpura in 1 of the 3 cases. The authors review the theories as to why these toxic symptoms appear. GARD, Galveston, Texas.

THE INTRAVENOUS ADMINISTRATION OF OXYGEN. EDWIN E. ZIEGLER, J. Lab. & Clin. Med. **27**:223 (Nov.) 1941.

An apparatus is described for the intravenous administration of oxygen. It is felt to be safe and much cheaper to operate than other oxygen therapy units. No clinical case reports are given, but patients seem not to mind this method of oxygen therapy as much as some others. GARD, Galveston, Texas.

DOSAGE INTERVAL IN SULPHAPYRIDINE ADMINISTRATION. R. ANDREW, M. J. Australia **2**: 612 (Nov.) 1941.

The incentive to this study was the field difficulty experienced by medical officers in insuring frequent dosage for soldiers in transit from forward areas. Three groups of patients were studied, who were given 9, 6 and 4 Gm. of sulfapyridine on successive days at intervals of four, twelve and twenty-four hours. Approximately equivalent concentrations of sulfapyridine in the blood were obtained in the three groups. The author concludes that: (1) administration every twelve or twenty-four hours is practicable for immediate prophylactic use and during the evacuation of casualties, and (2) dosage every twelve hours has advantages in military hospitals and in civil practice. GONCE JR., Madison, Wis.

DISEASES OF CHILDREN. WILFRID SHELDON, Practitioner **147**:636 (Oct.) 1941.

The author, writing of conditions in Britain, stresses the importance of breast feeding during the emergency period, even though complementary feeding is necessary. The government now has "nationalized" all dried milk products under one brand, which is considered a distinct advance.

There is considerable difficulty in securing orange juice, so that recourse is had to tomatoes, black currants, potatoes and ascorbic acid tablets.

Reduction in the number of hemorrhages in the newborn by the prophylactic administration of synthetic vitamin K to the mother is emphasized.

A résumé of the treatment of pyloric stenosis adds nothing except to point out the advantages of the relatively nontoxic methyl nitrate salt of atropine as part of the medical treatment.

A great increase in the incidence of scabies has arisen during the war, owing partly to the evacuation of infected children from cities into rural areas and partly to the overcrowded condition of sleeping quarters occasioned by air raids. Traditional sulfur therapy is used, but a somewhat less tedious method is the use of benzyl benzoate, methyl spirit and soft soap in equal parts prepared as a lotion to be painted on the skin, allowed to dry for twenty-four hours and removed by an ordinary bath.

The use of phenothiazine in 1 Gm. daily doses for children under 4 years of age and 2 Gm. for children from 4 to 8 years is advocated for threadworm infection.

GELSTON, San Francisco.

Book Reviews

Allgemeine Neurosenlehre; Biologie, Psychoanalyse und Psychohygiene leib-seelischer Störungen. In zweiundzwanzig Vorlesungen. By Rudolph Brun. Price, paper, 26 francs; cloth, 29 francs. Pp. 475, with 5 illustrations. Basel: Benno Schwabe, 1942.

On page 245 of this volume of 475 pages, the author proclaims that the very laws underlying, according to Freud, the neurotic conflict of drives and impulses may be shown as functioning in a similar way in the total field of biology, even with regard to the reflexes. The dynamic and economic principles as Freud has introduced them into the psychology of instincts have to be regarded as general biologic laws. And on page 409 appears the statement: "There is no real opposition between the physiologic and psychologic concept regarding the problems of the neuroses. Both illuminate nothing but different aspects of the same facts."

A psychoanalytic treatise on the neuroses by a former disciple of Monakow and Forel presents the reader with the rare pleasure of following a biologically trained great mind in its attempt to base freudian psychology on natural laws. Throughout this book the author strives at the recognition, and more, the coordination of organic-physiologic and functional-psychologic factors in the structure of neuroses. Four chapters deal with the organic factors in etiology and symptomatology of the "actual neuroses," neurasthenia and anxiety neurosis as well as with the neuropathologic theories of hysteria.

Heredity is discussed in a special chapter, and in four chapters more the author explains the biology of instincts, drives and impulses, comprising the normal and abnormal development of the instinctual life.

The mechanisms at work in the formation of symptoms, as clearly seen in hysteria, phobias and compulsion neuroses, are explained in seven chapters, and the instinctual conflict in the genesis of psychoneuroses is demonstrated with particular care. Valuable contributions to the question of mixed types of neuroses as well as character neuroses and war and accident neuroses and, finally, a lively picture of the structure of neuroses, of the neurotic in his world and of the prophylaxis, psychic hygiene and therapy of the neuroses terminate the book.

No doubt many a criticism could be raised against more than one of Brun's statements and deductions. But this is not the least stimulating and useful quality of this refreshing and entertaining book.

Psychotherapy in Medical Practice. By Maurice Levine, M.D. Price, $3.50. Pp. 320, with no illustrations. New York: The Macmillan Company, 1942.

Here is a book on psychiatry for all physicians. Written by a man who knows psychiatry, it is presented in a language which any one can understand. The various forms of mental ill health are described, together with the treatment which can be carried out by the general physician. The author also discusses the types of disorders which can be treated safely in the home and the physician's office and those which are best treated in a sanatorium and under the care of a psychiatrist.

The titles of the chapters epitomize the contents of the book. They are: "Methods of Psychotherapy," "Methods for the General Practitioner," "Advanced Methods for the General Practitioner," "Methods for the Specialist," "Suicide Risks," "The Choice of Cases," "Sex and Marriage," "Basic Attitudes Towards Children," "Normality and Maturity" and "Suggestions for Further Reading."

The chapter on the basic attitudes toward children deals with the attitudes of parents and others toward children. The author's viewpoint is that "it is better to foster the goal of growth and development and improvement rather than the goal of perfection." Like most discussions on psychiatry or psychology of childhood, this book does not give specific information on how one should apply the general information when dealing with specific problems of infant and child rearing. The chapters dealing with mental ill health in adults are, therefore, the most valuable ones.

War Medicine: A Symposium. Edited by W. S. Pugh, E. Padolsky and D. D. Runes. Price, $7.50. Pp. 565, with 108 illustrations and 13 tables. New York: Philosophical Library, 1942.

This book is a symposium on those aspects of medicine and surgery which are of particular importance in wartime. Over fifty subjects are included, all written by different authors. As is fitting, many members of the British and United States armed forces are included among the contributors.

The material is presented under three general headings: surgery, general medicine, and aviation and naval medicine. Under the first are discussed the usual topics of wounds, shock, burns and infections. There are two particularly interesting and important chapters, on the "Wounding Mechanism of High Velocity Missiles" and "Blast and Concussion." The section on general medicine contains a variety of chapters, some of the best being "Treatment of Gas Casualties," "Chigger and Jigger Bites" and several on psychiatric subjects.

The most interesting and informative section is that on aviation and naval medicine. This is essentially a discussion of different aspects of the problems of high altitude and deep sea diving as regards their effect on the human organism. Much new or previously not readily available information is presented.

In summary, there are some good chapters in this book. Much of the material, however, is not new and is more superficially presented than limitations of space would seem to require.

Lehrbuch der allgemeinen Kinderpsychiatrie. By M. Tramer, M.D., Ph.D., Privatdozent, University of Bern, and Director of Psychiatry, Children's Division, Kontonal-Solthurn in Gotthelf-House. Price, 26 Swiss francs, paper; 29 Swiss francs, cloth. Pp. 485. Basel: Benno Schwabe & Co., 1942.

In content and arrangement of the material this book has no counterpart in the English language. Comparison with other texts on the subject are consequently impossible. The table of contents alone occupies seven and one-half pages of 8 point type, a reliable indication of the variety of subjects treated in the volume. The author for many years has taken a keen interest in child psychiatry and as editor of the *Zeitschrift für Kinderpsychiatrie* (*Journal de Psychiatrie Infantile*) has exercised undisputed leadership in the field on the continent of Europe.

Professor Tramer logically assumes that in order to recognize a psychopathologic problem in childhood and youth the physician must be thoroughly familiar with the many physical, emotional and intellectual phases which characterize the normal organism. In harmony with this assumption the author offers a comprehensive description of these essential features of development, discussing structure of organs, psychic function, etc.; depicting anatomic deviations generally recognized as stigmas of degeneration, and tracing the well recognized genesis of the emotions through the various stages of growth to and well byeond adolescence. The many hereditary and environmental influences on the formation of the personality receive attention from the psychobiologic as well as from the psychoanalytic viewpoint. While the leaning is toward the latter, the author does not leave the impression of a dogmatic attitude.

The pediatrician who seeks special and detailed knowledge in child psychiatry will find the volume instructive and interesting. The physician, however, who is satisfied with a practical working knowledge of the intellectual and emotional processes of childhood and youth will have to wade through much theoretic material before finding the specific information which he may desire. In the reviewer's opinion he will derive more benefit with less strain from the expositions of Leo Kanner, Esther Loring Richards or Bert Beverly or from other American works of a similar nature.

Advances in Pediatrics. Volume I. Edited by Dr. Adolph G. De Sanctis. Price, $4.50. Pp. 306, with 41 illustrations. New York: Interscience Publishers, Inc., 1942.

Unlike the "Yearbook of Pediatrics," in which a great mass of material is covered in a rather brief manner, the content of this book is confined to relatively few subjects which are discussed thoroughly in a series of scholarly essays. It is a stimulating and satisfying contribution to pediatric literature and gives the reader an excellent foundation on which to build further from his own observations. It is provided with both author and subject indexes.

Toxoplasmosis is presented by Albert B. Sabin; virus diseases, by Horace L. Hodes; chemotherapy, by Benjamin W. Carey; electroencephalography, by Norman Q. Brill; vitamin K in the newborn period, by Henry G. Poncher; persistent ductus arteriosus, by Robert E. Gross; the premature infant, by Abraham Tow; tuberculosis, by Waldo E. Nelson; endocrinology, by Murray B. Gordon, and short abstracts of other subjects, by Adolph G. de Sanctis and George E. Pittinos.

Preliminary Report on Children's Reactions to War, Includng a Critical Survey of the Literature. Monograph from New York Hospital and the Department of Psychiatry, Cornell University Medical School. Published, 1942, with a grant from Josiah Macy, Jr., Foundation. By Dr. J. Louise Despert. Price, not given. Pp. 102, with no illustrations.

In this monograph the author has analyzed the large amount of material which has been written on the reaction of children to war and interprets the reports in terms of personality

studies of normal children in the United States. Since many articles have been written by untrained observers and reflect personal prejudice rather than scientific facts, their conclusions are often conflicting.

In general, the reactions of children, both in the United States and abroad, reflect the security of parents and the home more than any other single factor. Children with anxieties before the war naturally display greater anxieties because of it. In other words, insecurities because of the war depend on the age of the child, his mental health before the war and the danger to which he is exposed; all of these reactions reflect the attitudes of parents and the home situation.

Dr. Colwell's Daily Log for Physicians, 1943. Price, $6.00. Champaign, Ill.: Colwell Publishing Company, 1942.

This is the usual helpful account book for the physician's desk. It has the many advantages which the former editions have possessed and should be a handy accessory for the busy physician.

News and Comment

GENERAL NEWS

The American Board of Pediatrics, Inc.—Because of the large number of applicants for examination in the fall of 1943, two oral examinations will be held: one in New York, on November 20 or 21, and one in Cincinnati, on December 11. Written examinations will be given locally, under a monitor, on October 8.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Charles F. McKhann, University Hospital, Ann Arbor, Mich.

Canadian Committee:

Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. L. G. Parsons, 58 Calthorpe Rd., Five Ways, Birmingham, England.
Secretary: Dr. Donald Paterson, 27 Devonshire Pl., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14a, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p.m.

*Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialkstr., Tel Aviv.
Secretar: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Angel A. Aballí Arellano, 17 No. 609 Vedado, Habana.
Secretary: Dr. Julio G. Cabrera Calderin, Hospital Mercedes L y 21 (Vedado), Box 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico City.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico City.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. E. Santos Mendoza, Venezuela.
Secretary: Dr. P. Oropeza, Hospital de Niños, Caracas, Venezuela.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time; 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Nicolas Leone Bloise, Avenida Agraciada 2496, Montevideo.
Secretary: Dr. Héctor Mourigan, Avenida Agraciada 1464, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edward C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Region IV. Meeting cancelled.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. R. R. Struthers, 906 Drummond Medical Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Joseph A. Johnston, Henry Ford Hospital, Detroit.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. M. L. Bridgeman, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. C. G. Ashley, 833 S. W. 11th Ave., Portland, Ore.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 2:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. George M. Lyon, 955–4th Ave., Huntington, W. Va.
Secretary: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. E. H. Christopherson, 420 Walnut Ave., San Diego.
Secretary: Dr. William C. Deamer, University of California Hospital, San Francisco.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association meeting at time of convention.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Frank Schley, 1301 Broadway, Columbus.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. Ernest Caulfield, 683 Asylum Ave., Hartford.
Secretary: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. S. G. Wolfe, 1560 Line Ave., Shreveport.
Secretary-Treasurer: Dr. W. C. Rivenbark, 1448 Louisiana Ave., New Oleans.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J Orr, 135 Linwood Ave., Buffalo.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1942.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Charles F. McKhann, University Hospital, Ann Arbor.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. Elmer W. Bantin, 440 Aguila Court Bldg., Omaha.
Secretary-Treasurer: Dr. John M. Thomas, 301 N. 49th St., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. Forris E. Chick, 2325 University Ave., New York.
Secretary: Dr. Jacob H. Turner, 121 W. 197th St., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Charles A. Weymuller, 85 Pierrepont St., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of October, November, February, March and April.

Buffalo Pediatric Society

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. Heyworth N. Sanford, 952 N. Michigan Ave., Chicago.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. Lloyd K. Felter, 3144 Jefferson Ave., Cincinnati.
Secretary: Dr. Leo S. Friedman, 3586 Reading Rd., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Bruce A. Knickerbocker, 3403 Hall St., Dallas, Texas.
Secretary-Treasurer: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Hugh Lewis, Detroit, Mich.
Secretary: Dr. John J. Pollack, 622-26 Maccabees Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

[illegible]
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Mount Pleasant.
City.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Elmer W. Bantin, 440 Aguila Court Bldg., Omaha.
Secretary-Treasurer: Dr. John M. Thomas, 301 N. 49th St., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Hampshire Pediatric Society

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Irwin Schiff, 658 Eastern Parkway, Brooklyn.
Secretary: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144-38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Spigel, 2647 Connecticut Ave., Washington, D. C.
Secretary-Treasurer: Dr. Perry W. Gard, 2520 Woodley Rd., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Alfred Langmann, 108 E. 68th St., New York.
Secretary: Dr. Edith M. Lincoln, 600 Park Ave., New York.
Place: New York Academy of Medicine, 2 E, 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Northwestern Pediatric Society

President: Dr. Arild E. Hansen, University of Minnesota, Minneapolis.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

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Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo, N. Y.
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Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn. Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Physicians and Surgeon's Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Irwin Schiff, 658 Eastern Parkway, Brooklyn.
Secretary: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

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Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144-38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Spigel, 2647 Connecticut Ave., Washington, D. C.
Secretary-Treasurer: Dr. Perry W. Gard, 2520 Woodley Rd., Washington, D. C.
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Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
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Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
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Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Northwestern Pediatric Society

President: Dr. Arild E. Hansen, University of Minnesota, Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Theodore S. Wilder, Greene and Coulter Sts., Germantown, Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday in March, May, October and December.

Pittsburgh Pediatric Society

President: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, 125 De Soto St., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Maurice J. Lonsway, 3720 Washington Blvd., St. Louis.
Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.
Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Paul Hamilton, 1635 Chelsea Rd., San Marino, Calif.
Secretary: Dr. Helen Hopkins, 3875 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.

INDEX TO VOLUME 65

The asterisk (*) preceding the page number indicates an original article. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews and Obituaries are indexed under the letters B and O, respectively.

Abdomen: See also Gastrointestinal Tract
allergic reactions in, 514
Abnormalities and Deformities: See also Arachnodactyly; Palate, cleft; Twins; and under names of diseases, organs and regions, as Brain; Cornea; Cranium; Duodenum; Esophagus; Extremities; Fingers and Toes; Heart; Iris; Kidneys; Lungs; Neck; Ribs; Skin; Stomach; etc.
congenital malformations induced in rats by maternal nutritional deficiency; cleft palate, *882
etiology of disturbances of development, 939
Abscess: See also under names of organs and regions, as Temporal Bone; etc.
peritonsillar, tonsillectomy in cases of, 501
Acid, Acetylsalicylic: See Rheumatic Fever
Amino: See Amino Acids
Ascorbic: See Ascorbic Acid
Cevitamic: See Ascorbic Acid
effects of various urinary antiseptics on strains of Escherichia coli; sulfathiazole; urinary acidity, mandelic acid, methenamine and methenamine mandelate; relative value of sulfathiazole, sulfadiazine, sulfapyridine sulfacetimide and sulfanilamide, *399
fatty; effect of certain fats and unsaturated fatty acids on utilization of carotene, 167
Nicotinic: See Nicotinic Acid
Pantothenic: See Vitamins, B
Tannic: See Burns
Acid-Base Equilibrium: See also Acidosis
acid-base balance, renal function and gastric secretion during hypochloremia in dog, 803
Acidosis: See also Acid-Base Equilibrium
intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome); report of case in which increased urinary organic acids were detected and identified, with review of literature, *81
Acne vulgaris, endocrine factors in, 514
Acromegaly, studies of calcium and phosphorus metabolism; influence of pituitary gland, 803
Adamantinoma, hypophysial, 948
Addison's Disease, case of, 821
vitiligo; creatine metabolism, 676
Adenoids, postoperative hemorrhages from tonsils and adenoids, 673
Adipose Tissue: See Fat; Obesity
Adolescence, athletic activity at puberty with reference to cardiac and tuberculous patient, 498
basal metabolism of normal children from 13 to 15 years old, inclusive, *845
Calmette vaccination of young persons, 812
certain problems of puberty and adolescence, 485
endocrine problems in, 510
examination of adolescent female, 485
heart and vascular system during puberty, 671
menstrual abnormalities of, 509
obesity in relation to puberty, 482
physiologic changes incident to puberty, 328
sexual education of adolescent, 508
standard metabolism of, 481
tumors of brain in children and in adolescents; clinical and anatomic survey of 92 verified cases, *604
what to do about fat child at puberty, 482
Adrenal Preparations, clinical use of adrenal cortex extract in celiac disease, 505
Adrenals, effect of testosterone propionate on mitotic activity of adrenals in intact immature female rat, 349
hemorrhage; Waterhouse-Friderichsen syndrome on Isthmus of Panama, *426
tumor; Cushing's syndrome in children; review of literature and report of case, *593
Age, 1937-1938 epidemic of acute anterior poliomyelitis in New South Wales, with reference to change in age incidence, poliomyelitis during pregnancy and poliomyelitis following tonsillectomy, 807
Old: See Old Age
Air Passages: See Respiratory Tract
Albers-Schönberg's Disease: See Osteosclerosis fragilis
Albumin: See under Blood, proteins; Proteins
Allergy: See Anaphylaxis and Allergy; Asthma; Food, allergy; etc.
Altitude, influence of high altitude flights on children with whooping cough, 491
keratoconjunctival lesions observed at high altitudes in Bolivia, 951
Amaurosis: See Blindness
Amblyopia: See Blindness
Amentia: See Feeblemindedness; Idiocy
Amino Acids: See also Proteins
intake by breast milk fed infants and amino acid composition of cow's milk and human milk, 168
Anaphylaxis and Allergy: See also Asthma; Food, allergy; Tuberculosis, allergy; etc.
allergic pathogenesis of acute nephritis, 949
allergic reactions in abdomen, 514
concept of atopy in light of recent investigations, 352
enuresis of allergic origin; report of 2 cases, 185
immunity to tetanus induced by third dose of toxoid 2 years after basic immunization, based on study of 31 allergic children, *873
studies on anaphylaxis in mouse, 190
Anastomosis: See Legs, blood supply
Andersen, D. H.: Serum cholesterol values for infants and children, *858
Anderson, G. K.: Streptococcic antifibrinolysin in newborn infants; true and false tests, *60
Anderson, N. A.: Causes of prematurity; influence of race and sex on duration of gestation and weight at birth, *523
Androgens, absorption of pellets of crystalline testosterone, testosterone propionate, methyl testosterone, progesterone, desoxycorticosterone and stilbestrol implanted in rat, 186
effect of testosterone propionate on bone growth and skeletal maturation of normal and castrated male rats, 349
effect of testosterone propionate on creatinuria of experimental hyperthyroidism in male and female monkeys, 186
effect of testosterone propionate on mitotic activity of adrenals in intact immature female rat, 349
effect of testosterone propionate on reproduction in female, 186
effects of large amounts of androgen on testes of prepuberal rat, 186
structure of Bowman's capsule in castrate and testosterone-treated male mice as index of hormonal effects on renal cortex, 348
Anemia, acute hemolytic, 813
acute hemolytic, from sulfonamides, 813
acute hemolytic, in case of acute hepatitis, 814

Anemia—Continued
Chlorotic: See Chlorosis
Cooley's: See Anemia, erythroblastic
cure of congenital aplastic anemia (Benjamin type), 499
erythroblastic; familial blood studies in cases of Mediterranean (Cooley's) anemia; diagnosis of trait, or mild form of disease, *681
erythroblastic; pathogenesis of Cooley's anemia, 499
erythroblastic; results of splenectomy in 2 cases, 813
erythroblastosis foetalis (acute hemolytic anemia of newborn); preliminary report, *571
Mediterranean: See Anemia, erythroblastic
secondary, 498
serum cholesterol values for infants and children, *858
splenic; Gaucher's disease in infant, 813
toxic reaction to sulfapyridine, 954
vitamin K in other than hemorrhagic diseases, 339
Anergy: See Tuberculosis
Anesthesia, effects of morphine on labor, 332
effects of scopolamine on fetus, 332
Aneurysm, intracranial, 506
Angina: See also Throat
diphtheritic, Manzullo test in early diagnosis of, 489
Vincent's: See Fusospirochetosis
Angioma, giant, of mesentery, 178
vascular birthmarks, 352
vascular malformations and vascular tumors involving spinal cord; pathologic study of 46 cases, 178
Anodontia: See Teeth
Anomalies: See Abnormalities and Deformities; and under names of organs and regions
Anthropometry: See Adolescence; Children; Growth; etc.
Antifibrinolysis: See Blood, fibrin
Antigens and Antibodies: See under specific antigens and reactions, as Typhoid; etc.
Antisepsis and Antiseptics: See also Sterilization
effects of various urinary antiseptics on strains of Escherichia coli; sulfathiazole; urinary acidity, mandelic acid, methenamine and methenamine mandelate; relative value of sulfathiazole, sulfadiazine, sulfapyridine, sulfacetimide and sulfanilamide, *399
Antiserum: See Diphtheria; etc.
Antithrombin: See Blood, coagulation
Antitoxin: See under Diphtheria; Scarlet Fever; Tetanus; Whooping Cough
Aphthae: See Stomatitis
Apparatus: See also Instruments
intravenous administration of oxygen, 955
rate of secretion of parotid glands in normal children; measurement of function of autonomic nervous system, *455
Arachnodactyly, histologic eye findings in, 938
Armies: See Medicine, military
Arms: See Extremities; Forearms; Radius; etc.
Arrhythmia, auricular paroxysmal tachycardia in infancy, 175
paroxysmal tachycardia in 2 month old infant with ventricular rate of 350, *582
Arteries: See Aneurysm; Blood, pressure; Periarteritis; Thrombosis; etc.
Coronary: See Coronary Vessels
Arthritis, band-shaped opacity of cornea associated with juvenile atrophic arthritis, 187
frequency of chorea and acute polyarthritis in children during last 20 years in Stockholm, 346
influence of hyperpyrexia on ascorbic acid concentration in blood, 485
serous meningitis, ulcerative stomatitis and infectious arthritis with epiphysiolysis of left hip joint in scarlet fever, 491
Ascorbic Acid: See also Scurvy
comparative costs of vitamin C in fresh and commercially canned fruit and vegetable juices, 171
Ascorbic Acid—Continued
content of human milk, 806
content of placenta, blood from umbilical vein and colostrum, 806
effects of sodium diphenyl hydantoinate (dilantin) on blood ascorbic acid level in guinea pigs, 170
effects of vitamins B_1 and C on endocrine equilibrium in infancy, 805
influence of hyperpyrexia on ascorbic acid concentration in blood, 485
Asthma: See also Anaphylaxis and Allergy
asthma reflex originating in tonsil, 672
Athetosis; cerebral palsy problem, 945
Athletics; athletic activity at puberty with reference to cardiac and tuberculous patient, 498
Atopy: See Anaphylaxis and Allergy
Atrophy: See also under names of organs and regions, as Bones; Nerves, optic; etc.
Infantile: See Celiac Disease
Muscular: See also Dystrophy, muscular
muscular; disuse atrophy of skeletal muscles, 187
Auricular Fibrillation: See Arrhythmia
Avitaminosis: See under Vitamins; and under names of deficiency diseases, as Beriberi; Scurvy; etc.
Azosulfamide: See Streptococci

B C G: See Tuberculosis
Bacilli: See Bacteria
Bacillus Welchii: See Bacteria, aerogenes capsulatus
Backward Children: See Nervous and Mental Disabilities
Bacteremia: See under Staphylococci; Streptococci; etc.
Bacteria: See also Diphtheria; Pneumococci; Typhoid; Viruses; etc.
aerogenes capsulatus; diabetic coma, acute pancreatitis and Bacillus welchii peritonitis, *36
Bacillus pyocyaneus meningitis following pneumoencephalography, *912
Bordet-Gengou: See Whooping Cough
Calmette-Guérin: See Tuberculosis
coli; effects of various urinary antiseptics on strains of Escherichia coli; sulfathiazole; urinary acidity, mandelic acid, methenamine and methenamine mandelate; relative value of sulfathiazole, sulfadiazine, sulfapyridine, sulfacetimide and sulfanilamide, *399
coli; quantitative comparisons of activity of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine against Escherichia coli in vivo and in vitro, 329
Corynebacteria: See under Diphtheria
Diphtheria: See under Diphtheria
Dysentery: See Dysentery
Flexner's: See Dysentery
Fusiformis: See Fusospirochetosis
Hemophilus: See Influenza; Whooping Cough
Meningococci: See Meningococci
Pertussis: See Whooping Cough
Pfeiffer's: See Influenza
Salmonella: See Salmonella
Shiga's: See Dysentery
Sonne's: See Dysentery
Streptococci: See Streptococci
suppurative pericarditis due to Haemophilus influenzae type B; characteristic syndrome ushered in by symptoms of croup, *305
Tuberculosis: See Tuberculosis
Typhoid Group: See Bacteria, coli; Salmonella; Typhoid; etc.
Welchii: See Bacteria, aerogenes capsulatus
Bananas, use of plantain in infantile diarrhea, 804
Barbital and Barbital Derivatives, effect of sodium amytal on emptying time of normal human stomach, 343
Barlow's Disease: See Scurvy
Barré-Guillain Syndrome: See Nerves, roots
Battini, priority of Domenico Battini in description of congenital megacolon described as Hirschsprung's disease (1888), 819

Beard, J. W.: Enzymatic débridement in local treatment of burns; preliminary report, *909
Beetles, dermatitis venenata provoked by Coleoptera genus Paederus, 954
Benjamin, B.: Syndrome of cutaneous fragility and hyperelasticity and articular hyperlaxity, *247
Benjamin, H. R.: Basal heat production in relation to growth; longitudinal study on normal infants 6 to 20 months of age, *1
Calcium and phosphorus requirements of premature infants, *412
Benzyl Benzoate: See Scabies
Beriberi: See also Vitamins, B
prevention of, 171
Berman, R. A.: Excretion of 17-keto steroids by normal and by abnormal children, *364
Besnier-Boeck's Disease: See Sarcoidosis
Biggs, A. D.: Hypoplasia of mandible; report of case, with résumé of literature and suggestions for modified form of treatment, *440
Bile, extravasation; cholascos in childhood, 505
output of bile pigment by newborn infants and by older infants and children, *558
Bile Ducts: See also Biliary Tract; Gallbladder
choledochus cyst, 820
congenital atresia of, 504
Biliary Tract: See also Bile Ducts; Gallbladder; Liver
dwarfism and diabetes insipidus with congenital lesions of biliary tract in child of 6 years, 823
Bilirubinemia: See Blood, bilirubin
Biopsy: See Liver
Birth Injuries: See Newborn Infants
Premature: See Premature Infants
Stillbirth: See Stillbirths
Weight: See Newborn Infants
Birthmarks, Vascular: See Angioma
Bismuth and Bismuth Compounds, Therapy: See Tonsils
transfer of bismuth into fetal circulation after maternal administration of sobisminol, 940
Bitot Spots: See Conjunctiva; Cornea; Xerophthalmia
Black, Dr. Black honored, 480
Bladder: See also Urinary Tract
stones in urinary bladder in children; diagnosis and treatment in 7 cases, *591
Blennorrhea: See Gonorrhea
Blepharoptosis: See Eyelids, ptosis
Blindness: See also Ophthalmia neonatorum; Vision
congenital absence of septum pellucidum; case diagnosed encephalographically and associated with congenital amaurosis, 178
Blood: See also Hemoglobin and Hemoglobin Compounds; Leukocytes; etc.
ascorbic acid content of placenta, blood from umbilical vein and colostrum, 806
Bilirubin: See also Jaundice
bilirubin; clearance of bilirubin from plasma; measure of excreting power of liver, 804
Carotene: See also Vitamins, A
carotene; new test for hepatic insufficiency, 819
Cells: See also Blood, platelets; Leukocytes
cells; measurement of cell volume of blood by Evans blue dye method, 497
chlorides; acid-base balance, renal function and gastric secretion during hypochloremia in dog, 803
cholesterol; independence of serum cholesterol from exogenous cholesterol in infants and in children, *235
cholesterol; relation between thyroid function and cholesterol content of blood of infants and larger children, 821
cholesterol values for infants and children, *858
Circulation: See also Cardiovascular System; Heart; etc.
circulation, effects of patent ductus arteriosus on, 496
Blood—Continued
circulation; new objective circulation time (fluorescein method), 497
Coagulation: See also Blood, fibrin; Blood, fibrinogen; Blood, platelets; Blood, prothrombin
coagulation; erythrocytic sedimentation rate and Weltmann reaction in scarlet fever, 333
coagulation; formol-gel test during rheumatic fever of childhood; comparison with sedimentation rate and Weltmann reaction, 172
coagulation; globulin fraction in rabbit's plasma possessing strong clotting property, 941
coagulation; influence of diet of newborn infant on prothrombin index, 487
coagulation; micromethod for Weltmann reaction, 498
coagulation; prothrombin in newborn infant; further observations on prothrombin response to intravenous administration of water-soluble naphthoquinone, 487
coagulation; simple modification of Weltmann's coagulation reaction, 497
coagulation; thrombic activity of globulin fraction derived from rabbit plasma, 941
coagulation; use of rabbit thrombin as local hemostatic, 941
coagulation; Weltmann's coagulation reaction in serum in pulmonary and in extrapulmonary tuberculosis, 495
complementay power of blood serum in nutrition disturbances of infants, 804
Diseases: See also Anemia; Hemopoietic System; Leukemia; etc.
diseases and hemopoietic organs in infant, 813
effects of sodium diphenyl hydantoinate (dilantin) on blood ascorbic acid level in guinea pigs, 170
familial blood studies in cases of Mediterranean (Cooley's) anemia; diagnosis of trait, or mild form of disease, *681
fats and lipoids: See also Blood, cholesterol
fats and lipoids; studies on vitamin A; vitamin A and total lipid of serum in pneumonia, *712
fats and lipoids; total and fractional blood lipid levels in nephrotic syndrome, *770
fibrin; streptococcic antifibrinolysin in newborn infants; true and false tests, *60
Fibrinogen: See also Blood, coagulation
fibrinogen; plasma albumin, globulin and fibrinogen in healthy individuals from birth to adult life, 497
fibrinopenia in women with premature detachment of placenta, 814
Formation: See Hemopoietic System
Groups: See Blood, transfusion
influence of hyperpyrexia on ascorbic acid concentration in, 485
Injections: See Blood, transfusion
phosphatase; values of plasma phosphatase and blood phosphorus in healthy children born at term and in premature children, 499
phosphates; intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome); report of case in which increased urinary organic acids were detected and identified, with review of literature, *81
Phospholipids: See Brain, fats and lipoids
phosphorus; values of plasma phosphatase and blood phosphorus in healthy children born at term and in premature children, 499
picture, influence of tonsillectomy on, 815
Platelets: See also Purpura
platelets; improved method for estimation of quantitative and qualitative factors, 942
platelets; thrombocytopen; confirmatory report, 496
pressure, high; studies in experimental hypertension, 174
proteins; globulin fraction in rabbit's plasma possessing strong clotting property, 941

Blood—Continued
proteins; human cord serum globulin in modification and prevention of measles, 334
proteins; plasma albumin, globulin and fibrinogen in healthy individuals from birth to adult life, 497
proteins; stored protein in organism of infants and children; investigations to determine circulating reserve protein in blood plasma, 805
proteins; stored protein in organism of infants and children; normal total plasma protein values calculated from average water content of blood corresponding to age of child, 804
proteins; thrombic activity of globulin fraction derived from rabbit plasma, 941
Prothrombin: See also Blood, coagulation
prothrombin in newborn, 331
prothrombin; infarction of liver and hypoprothrombinemia; report of their association in newborn infant with failure of vitamin K therapy, *258
prothrombin; prevention of hypoprothrombinemia in newborn infants by treating pregnant woman with vitamin K, 333
sedimentation; effect of acetylsalicylic acid on sedimentation rate of erythrocytes in rheumatic fever, 338
sedimentation; erythrocytic sedimentation rate and Weltmann reaction in scarlet fever, 333
sedimentation; formol-gel test during rheumatic fever of childhood; comparison with sedimentation rate and Weltmann reaction, 172
sedimentation test and mastoiditis, 815
sedimentation tests in scarlet fever, 668
Sugar: See also Carbohydrates; Diabetes Mellitus; Insulin; etc.
sugar curves in chronic nutritional disturbances, 804
sugar; transitory hemiplegia associated with hypoglycemia in diabetic child with congenital heart disease, *73
Transfusion: See also Anemia
transfusion; accidental transmission of malaria (following transfusion), 172
transfusion; comparison of value of crystalloid solutions, whole blood and blood plasma in treatment of dehydration in infancy, 804
transfusion; cure of congenital aplastic anemia (Benjamin type), 499
transfusion; value in malignant diphtheria, 336
Vessels: See Cardiovascular System; Periarteritis; etc.
water content; stored protein in organism of infants and children; normal total plasma protein values calculated from average water content of blood corresponding to age of child, 804
Body Fluids: See Fluids
Weight: See also under Children; Obesity
weight; causes of prematurity; influence of race and sex on duration of gestation and weight at birth, *523
weight of healthy breast-fed infants during first year of life, 664
Boeck's Sarcoid: See Sarcoidosis
Bones: See also under names of bones
analysis in case of cystine disease, 484
atrophy; Morquio's disease, 351
Calcification: See Bones, growth
Deformities: See Abnormalities and Deformities; Poliomyelitis; Rickets; etc.
Diseases: See Osteomyelitis; etc.
effect of testosterone propionate on bone growth and skeletal maturation of normal and castrated male rats, 349
Fragility: See also Osteosclerosis fragilis
fragility; syndrome of blue sclera; its presence in 5 generations, 677
growth; influence of formative dental organs on growth of bones of face, 954
Bones—Continued
growth; variations in calcification pattern in epiphyses; their nature and significance, 821
Marble: See Osteosclerosis fragilis
marrow; diagnosis of cystine diseases (from sternal puncture), 484
marrow, morphologic development in fetal life, 803
marrow; normal sternal marrow in childhood, 803
marrow; value of sternal marrow aspiration as method of bone marrow biopsy, 174
multiple myelomas in child of 8 years, 950
osteogenic sarcoma, 351
principles of skeletal growth; teeth, 954
Book Reviews:
Advances in Pediatrics: Vol. 1; A. G. De Sanctis, 957
Allgemeine Neurosenlehre: Biologie, Psychoanalyse and Psychohygiene leib-seelischer Störungen. In zweiundzwanzig Vorlesungen; R. Brun, 956
Biological Action of Vitamins: Symposium; edited by E. A. Evans Jr., 679
Bonnie's Baby Brother and How He Grew; E. R. Montgomery, 518
Changes in Knee Joint at Various Ages; G. A. Bennett, H. Waine and W. Bauer, 517
Civilian Health in Wartime; F. R. Dieuaide, 679
Dr. Colwell's Daily Log for Physicians, 1943, 958
Epidemiologia del kala-azar infantil; J. Bolx Barrios, 194
Function of Orgasm; W. Reich, 826
Heredity, Food and Environment in Nutrition of Infants and Children; G. D. Scott, 517
Hospital Discharge Study: Volume I. Hospitals and Hospital Patients in New York City; N. R. Deardorff and M. Fraenkel, 192
Keep Them Human; C. M. Dixon, 194
Lehrbuch der allgemeinen Kinderpsychiatrie; M. Tramer, 957
Medical Parasitology; J. T. Culbertson, 354
Mental Illness: Guide for Family; E. M. Stern with collaboration of S. W. Hamilton, 679
Methods for Study of Personality in Young Children; edited by E. Lerner and L. B. Murphy, 679
Nutrition and Chemical Growth in Childhood: Volume I. Evaluation; I. G. Macy, 518
Preliminary Report on Children's Reactions to War, Including Critical Survey of Literature; J. L. Despert, 957
Principles and Practice of Medicine; W. Osler, edited and revised by H. A. Christian, 680
Psychotherapy in Medical Practice; M. Levine, 956
Sulfanilamide and Related Compounds in General Practice; W. W. Spink, 518
Vacunacion antituberculosa con el B. C. G.; A. Chattas, 194
Vitaminas en la alimentación del lactante; E. Jaso, 680
War Medicine: A Symposium; W. S. Pugh, E. Padolsky and D. D. Runes, 956
Borowsky, S.: Influence of minor dietary changes on frequency of infants' stools; study of effect of varying content of lactose, milk fat and thiamine, *827
Botallo's Duct: See Ductus Arteriosus
Bouillaud's Disease: See Rheumatic Fever
Bowels: See Intestines
Bowman's Capsule: See Kidneys
Brachyesophagus: See Esophagus, abnormalities
Braid, F.: Reports of Subcommittees of British Paediatric Association, 147
Brain: See also Nervous System; etc.
abnormalities; enormous myelomeningocele with fatal leakage, 506
action of formaldehyde on nervous system, 180
changes in pertussis with convulsions, 333

Brain—Continued
congenital absence of septum pellucidum; case diagnosed encephalographically and associated with congenital amaurosis, 178
Diseases: See also Encephalitis
diseases; choked disk in lead encephalopathy, 945
edema; cause of edema in tetany, 506
electroencephalography; cerebral electrical changes in experimental concussion, 947
electroencephalography; cortical frequency spectrum in epilepsy, 344
electroencephalography on children, *898
Encephalography: See Brain, roentgenography
Inflammation: See Encephalitis
Injuries: See also Head, injuries; etc.
injuries; cerebral electrical changes in experimental concussion, 947
injuries; experimental cerebral concussion, 946
roentgenography; Bacillus pyocyaneus meningitis following pneumoencephalography, *912
Sclerosis: See Sclerosis
study of dissociation and reorganization of cerebral function, 947
subcortical hematoma: surgical treatment, with report of 8 cases, 178
tumor simulating encephalitis, 345
tumors in children and in adolescents; clinical and anatomic survey of 92 verified cases, *604
Brakeley, E.: Late rickets, *314
Branchial Apparatus, clinical conditions arising from anomalies of maldevelopments of branchial arches or clefts, 814
Breast, effect of estrogens, gonadotropins and growth hormone on mammary glands of hypophysectomized rats, 348
Feeding: See Infant Feeding; Milk, human
"mammogen" and treatment of spayed hypophysectomized rats with lipoid extracts of cattle pituitary, 185
Milk: See Infant Feeding; Lactation; Milk, human
Brennemann, Joseph, Library, 327
British Paediatric Association, dosage of vitamin D; opinions on vitamin D requirements of infants and children, 158
neonatal mortality, 162
reports of Subcommittees of, 147
Broccoli, utilization of calcium of cauliflower and broccoli, 937
Bromide and Bromine, postinfectious encephalomyelitis; report of its occurrence following measles and vaccination for smallpox, with complicating bromide poisoning, *585
Bronchi, Dilatation: See Bronchiectasis
Diseases: See Bronchiectasis; Bronchitis; Bronchopneumonia
Bronchiectasis: See also Lungs, cysts
and atelectasis; experimental study concerning their relationship, 816
Bronchiolitis: See Bronchitis
Bronchitis, roentgenologic diagnosis of acute bronchiolitis (capillary bronchitis) in infants, 816
tracheobronchitis complicating grip and its treatment, 817
Bronchopneumonia: See also Pneumonia
pseudosyphilitic (pulmonary infiltrations with positive Wassermann reactions), 502
Brown, E. W.: Causes of prematurity; influence of race and sex on duration of gestation and weight at birth, *523
Bruce, J. W.: Erysipelas in infancy, *739
Burns, biochemical investigation of tannic acid and sulfanilamide treatment, 515
enzymatic débridement in local treatment; preliminary report, *949
Butler, A. M.: Excretion of 17-keto steroids by normal and by abnormal children, *344
Buttermilk, skim milk acidified with lactic or citric acid as adjuvant to, 170

Calcification: See Bones, growth; Epiphyses; Teeth; etc.
Calcium and Calcium Compounds, calcium and phosphorus metabolism in osteomalacia; pathogenetic role of pregnancy and relative importance of calcium and vitamin D supply, 511
calcium and phosphorus requirements of premature infants, *412
calcium requirement standards, 169
dependence of fetal growth and storage of calcium and phosphorus on parathyroid function and diet of pregnant rats, 167
effect of dietary calcium and phosphorus on assimilation of dietary fluorine, 167
studies of calcium and phosphorus metabolism; influence of pituitary gland, 803
Therapy: See Cranium, pressure in
utilization of calcium of cauliflower and broccoli, 937
Calculi: See Bladder; Gallbladder; Kidneys; Urinary Tract; etc.
Calmette-Guérin (BCG) Vaccine: See under Tuberculosis
Calories: See Infant Feeding
Calorimeter: See Metabolism
Cancer: See Sarcoma; and under names of organs and regions, as Colon; etc.
Canning and Canned Foods, comparative costs of vitamin C in fresh and commercially canned fruit and vegetable juices, 171
Capon, N. B.: Neonatal mortality, 162
Carbohydrates: See also Lactose; etc.
value of complex carbohydrates in diets of normal children, *195
Carbuncle, Renal: See Nephritis
Cardiovascular System: See also Heart; etc.
heart and vascular system during puberty, 671
Caries, Dental: See Teeth
Carotene: See also Vitamins, A
effect of certain fats and unsaturated fatty acids on utilization of, 167
Carriers: See Diphtheria, carriers; etc.
Cassie, E.: Reports of Subcommittees of British Paediatric Association, 147
Castration, effect of testosterone propionate on bone growth and skeletal maturation of normal and castrated male rats, 349
Catabolism: See Metabolism
Cataract, congenital annular, 512
genuine tetanic nutritional cataract, 953
multilamellar, with globules; report of case, 822
Catarrh: See under Mastoiditis
Cathartics are unimportant, 189
Caulfield, E.: Pediatric aspects of Salem witchcraft tragedy; lesson in mental health, *788
Cauliflower, utilization of calcium of cauliflower and broccoli, 937
Celiac Disease, clinical use of adrenal cortex extract, 505
Cells: See also Blood, cells; etc.
division; effect of testosterone propionate on mitotic activity of adrenals in intact immature female rat, 349
production of cytoplasmic inclusions in liver cells of rats injected with certain proteins, 199
Cerebrospinal Fever: See Meningitis
Cerebrospinal Fluid, proteins; Guillain-Barré syndrome ("infectious polyneuritis") and acute anterior poliomyelitis, *631
staphylococcus antitoxin in pleural exudates and spinal fluid, 816
Cerebrum: See Brain
Cevitamic Acid: See Ascorbic Acid
Chalkley, T. S.: Erysipelas in infancy, *739
Chemotherapy: See under names of diseases and chemotherapeutic agents, as Meningitis; Sulfanilamide and Sulfanilamide Derivatives
Chest: See Thorax
Chickenpox, fatal case of encephalitis following varicella, 668
Child Guidance: See Mental Hygiene

Child Welfare: See also Infant Welfare
Subcommittee on Maternity and Child Care, 680
Children: See also Infants; Newborn Infants; Pediatrics; Schools; etc.
developmental changes in attitude as 1 factor determining energy output in motor performance, 181
diseases of, 955
Growth: See Growth
measures which characterize individual during development of behavior in early life, 181
Nervous and Mental Disabilities: See Nervous and Mental Disabilities
Nutrition: See Diet and Dietetics; Nutrition; Schools; etc.
output of bile pigment by newborn infants and by older infants and children, *558
relation between development of behavior and pattern of physical growth, 181
size discrimination in, 182
sulfadiazine; review of its use in treatment of children, *702
Chloroleukemia: See Chloroma
Chloroma; myeloid chloroleukemia, 943
Chlorosis; has chlorosis really disappeared? 814
Choanae: See Nose
Choked Disks: See Neuritis, optic
Cholascos: See Bile, extravasation
Cholelithiasis: See Gallbladder, calculi
Cholera, Infantile: See Diarrhea
Cholesteremia: See Blood, cholesterol
Cholesterol, in Blood: See Blood, cholesterol independence of serum cholesterol from exogenous cholesterol in infants and in children, *235
Chondrodysplasia: See Dyschondroplasia
Chordoma, 191
Chorea, frequency of chorea and acute polyarthritis in children during last 20 years in Stockholm, 346
Sydenham's; preliminary report of 3 cases successfully treated with vitamin B_6, 178
Choriomeningitis, lymphocytic; 2 human fatalities following unusual febrile illness, 506
Chorionic Gonadotropin: See Gonadotropins
Christian-Schüller Syndrome: See Schüller-Christian Syndrome
Ciliary Body: See Uvea
Cinematography: See Moving Pictures
Circulation: See Blood, circulation
Cirrhosis: See Liver, cirrhosis
Clarke, H. T.: Intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome); report of case in which increased urinary organic acids were detected and identified, with review of literature, *81
Cleft Palate: See Palate, cleft
Coburn, A. F.: Nutrition as conditioning factor in rheumatic state, *744
Cod Liver Oil, rickets and cod liver oil prophylaxis, 806
Colds: See Respiratory Tract, diseases
Coleoptera: See Beetles
Colitis, hemorrhagic rectocolitis in girl of 12 years, 674
ulcerative, relation of nasopharyngitis to, 503
Collis, W. R. F.: Neonatal mortality, 162
Collodion Disease: See Ichthyosis
Coloboma: See Iris; Nerves, optic
Colon: See also Gastrointestinal Tract; Intestines
carcinoma with report of case, 344
dilatation; megacolon and its treatment with sympathectomy, 820
dilatation; priority of Domenico Battini in description of congenital megacolon described as Hirschsprung's disease (1888), 819
dilatation; surgical treatment of 10 patients with congenital megacolon, 820
Invagination: See Intussusception
polyps, 2 cases of, 819
Colostrum, ascorbic acid content of placenta, blood from umbilical vein and colostrum, 806
Coma: See also under Diabetes Mellitus
diabetic, acute pancreatitis and Bacillus welchii peritonitis, *36
Communicable Diseases: See also Immunity; Measles; Meningitis; Syphilis; etc.
immunization against common communicable diseases, 939
some aspects of common contagious diseases, 334
Complement Fixation: See Influenza
Concussion: See Brain, injuries
Conjunctiva, Bitot's spots in Trinidad, 951
Conjunctivitis: See also Keratoconjunctivitis; Ophthalmia
Granular: See Trachoma
primary diphtheritic conjunctivitis in infant, 808
Contagious Diseases: See Communicable Diseases
Convalescent Serum: See Measles; Poliomyelitis; etc.
Convulsions: See also Epilepsy; Tetany; etc.
changes in brain in pertussus with convulsions, 333
reexamination of children suffering from convulsions, 949
Cook County Hospital, pneumonia of infants, season of 1941, 342
Cooley's Anemia: See Anemia, erythroblastic
Cooper, G. R.: Enzymatic débridement in local treatment of burns; preliminary report, *909
Cornea, abnormalities; congenital malformations; strands replacing both superior rectus muscles, absence of inferior rectus muscles, microcornea and coloboma of iris; new operative method to correct hypertropia of eyeballs, 822
band-shaped opacity associated with juvenile atrophic arthritis, 187
Bitot's spots in Trinidad, 951
corneoscleral cyst, 513
molluscum contagiosum corneae, 515
Pannus; See Trachoma
Coronary Vessels, coronary calcification and thrombosis in infant, 175
Correction in transcript of article by Emilio Soto Pradera, Enrique Fernandez and Oscar Calderin entitled "Coconut Water: A Clinical and Experimental Study" (Am. J. Dis. Child. **64**: 977 [Dec.] 1942), 327
Corynebacteria: See under Diphtheria
Cottonseed Oil: See Oil
Cram, E. B.: Studies on oxyuriasis; summary and conclusions, *46
Cranium: See also Temporal Bone; etc.
abnormalities; lacunar skull due to pressure, 511
hereditary craniofacial dysostosis, 806
pressure in; calcium therapy in control of intracranial pressure with reference to newborn infant, 331
Creatine and Creatinine, Addison's disease, vitiligo, creatine metabolism, 676
in Urine: See under Urine
relation of high and low urea clearances to inulin and creatinine clearances in children with nephrotic syndrome, 949
Creatinuria: See under Urine
Cretinism, 350
Crime and Criminals, children's reactions to movie horrors and radio crime, 182
Cripples: See Abnormalities and Deformities
Croup, Diphtheritic: See Diphtheria, laryngeal
suppurative pericarditis due to Haemophilus influenzae type B; characteristic syndrome ushered in by symptoms of croup, *305
Crouzon's Disease: See Bones, growth
Cryolite: See Fluorides
Culture, pediatrician and intellectual culture, 516
Curtis, J.: Respiratory metabolism in infancy and in childhood; regulation of body temperature of premature infants, *376
Cushing's Syndrome: See Pituitary Body

Cutis Laxa: See Skin, abnormalities
Cystine and Cysteine; analysis of bones in case of cystine disease, 484
anatomic picture of cystine disease with dwarfism, 483
cystine diathesis, 483
diagnosis of cystine diseases (from sternal puncture), 484
dietary requirements for fertility and lactation, 937
enzymatic débridement in local treatment of burns; preliminary report, *909
ophthalmic changes in cystine disease, 512
Cysts: See under names of organs and regions, as Bile Ducts; Cornea; Larynx; Lungs; Neck; etc.

Dameshek, W.: Erythroblastosis foetalis (acute hemolytic anemia of newborn); preliminary report, *571
Output of bile pigment by newborn infants and by older infants and children, *558
Danlos-Ehlers Syndrome: See Joints; Skin, abnormalities
Davidson, H. B.: Congenital defect of skin in newborn infant, *916
Day, R.: Respiratory metabolism in infancy and in childhood; regulation of body temperature of premature infants, *376
Deaf-Mutism, 501
congenital auditory atresia; its plastic repair with functional restoration of hearing and phonation in deaf-mute, 673
Deafness: See also Hearing; Otitis Media
diagnostic significance of audiogram in cases of impaired hearing, 815
effect of noise on normal and impaired hearing, 816
in children, 499
statistics on etiologic examinations conducted at county school for deaf in Munich, 500
syndrome of blue sclera; its presence in 5 generations, 677
Death, Rate: See Infant Mortality
sudden, and Pott's disease in child of 4, 676
Defectives: See Feebleмindedness; Nervous and Mental Disabilities
Deficiency Diseases: See Diet and Dietetics; Nutrition; Vitamins; etc.; and under names of various diseases, as Beriberi; Scurvy; etc.
Deformities: See Abnormalities and Deformities; and under names of organs and regions
Dehydration, comparison between dehydration from salt loss and from water deprivation, 937
comparison of value of crystalloid solutions, whole blood and blood plasma in treatment, 804
Dementia: See Dementia Praecox; etc.
Dementia Praecox, diagnosis of juvenile psychosis, *868
treatment of childhood schizophrenia by metrazol shock modified by B-erythroidin, 949
Democracy and popular school (Argentina), 486
Demography: See Infant Mortality
Denenholz, E. J.: Studies in immunity to pertussis; effect of stimulating dose of Haemophilus pertussis vaccine, *730
Dentin: See Teeth
Dentition: See Teeth
Dermatitis: See also Eczema; etc.
Hemorrhagic: See Purpura
Medicamentosa: See under names of drugs
oak poisoning; cause removing treatment, 189
Rat-Bite: See Rat-Bite Fever
venenata provoked by Coleoptera genus Paederus, 954
Desoxycorticosterone Acetate: See Adrenal Preparations
Dextrose: See Blood, sugar; Carbohydrates
Diabetes Insipidus: See also Schüller-Christian Syndrome
and dwarfism with congenital lesion of biliary tract in child of 6 years, 823
Diabetes Mellitus: See also Blood, sugar
diabetic coma, acute pancreatitis and Bacillus welchii peritonitis, *36
enlargement of liver in diabetic children, 821
histone zinc insulin; its pharmacologic characteristics and its application in treatment of, 349
levulosuric diabetes, 676
transitory hemiplegia associated with hypoglycemia in diabetic child with congenital heart disease, *73
Diabetes, Renal; intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome); report of case in which increased urinary organic acids were detected and identified, with review of literature, *81
Diaphragm, Hernia: See Hernia, diaphragmatic
three cases of relaxatio diaphragmatica, 820
Diarrhea: See also Dysentery
acute diarrheal diseases; outbreak due to Salmonella typhi murium, 177
feeding of infants with citric acid milk, 805
infantile, use of plantain in, 804
Diathermy: See under names of diseases, organs and regions
Diathesis, Allergic: See Anaphylaxis and Allergy; Asthma
Hemorrhagic: See also Hemophilia; Purpura; Scurvy; etc.
hemorrhagic; infarction of liver and hypoprothrombinemia; report of their association in newborn infant with failure of vitamin K therapy, *258
hemorrhagic; K avitaminosis as cause in newborn and older infants, 332
Diaz, J. T.: Pseudohermaphroditism, *67
Dick Test: See Scarlet Fever
Diet and Dietetics: See also Food; Infant Feeding; Nutrition; Vitamins; under names of various diseases, as Diabetes Mellitus; and under names of foods, as Bananas; Milk; etc.
dietary requirements for fertility and lactation, 937
Teeth and Diet: See under Teeth
value of complex carbohydrates in diets of normal children, *195
Diethylstilbestrol: See Estrogens
Digestive System: See Gastrointestinal Tract; Intestines; Stomach; etc.
Digitalis, generalized muscular weakness as toxic reaction to, 515
Dihydrotachysterol: See Tetany
Diktyoma of ciliary body, 953
Dilantin: See Phenytoin
Diphtheria, active immunization against diphtheria, 810
carriers; treatment with sulfathiazole snuff, 335
"coccic diphtheroids," further form of diphtheroid angina, 809
diagnosis of slight myocardial insufficiency during convalescence from diphtheria, 808
discussion on active immunization; some present-day problems, 337
immunity against diphtheria and tetanus in animals, 489
immunity in animals, 490
laryngeal; intubation and tracheotomy for diphtheritic croup, 667
laryngeal; treatment of diphtheritic croup, 490
malignant, 490
malignant, value of blood transfusion in, 336
Manzullo test in early diagnosis of diphtheritic angina, 489
possibilities of active immunization and of specific therapy in, 667
primary diphtheritic conjunctivitis in infant, 809
reactions from toxoid, *519
tellurite reaction; further study on 100 consecutive cases at Steele Memorial Hospital, 335
Diplegia: See Paralysis
Directory of pediatric societies, 959

Disinfectants: See Antisepsis and Antiseptics; Sterilization
Disk, Optic: See Nerves, optic
Choked: See Neuritis, optic
Dislocations: See under names of joints
Diuresis and Diuretics: See Diabetes Insipidus; Kidneys; etc.
Diverticulum, Meckel's: See under Intestines
Dooley, S. W.: Agenesis of lung in infant, *776
Dropsy: See Edema; Hydrocephalus; etc.
Fetal: See Erythroblastosis, Fetal
Drugs: See also under names of individual drugs and under names of diseases
posology in pediatrics, 191
Ductus Arteriosus, patency in adults, 942
patent, effects on circulation, 496
Duodenum, abnormalities; duodenal atresia with case report of successful gastroenterostomy, 504
abnormalities; vomiting caused by anomaly of duodenum, 818
congenital obstruction, 343
intermittent vomiting following constriction of duodenum by mesenteric pedicle, 818
Ulcer: See Peptic Ulcer
Dust, resistance of influenza virus to drying and its demonstration on dust, 937
Duval, A. M.: Basal metabolism of normal boys and girls from 2 to 12 years old, inclusive; report of further study, *834
Basal metabolism of normal children from 13 to 15 years old, inclusive, *845
Dwarfism: See also Cretinism
analysis of bones in case of cystine disease, 484
anatomic picture of cystine disease with dwarfism, 483
and diabetes insipidus with congenital lesion of biliary tract in child of 6 years, 823
cystine diathesis, 483
diagnosis of cystine diseases (from sternal puncture), 484
excretion of 17-keto steroids by normal and by abnormal children, *364
ophthalmic changes in cystine disease, 512
Dyschondroplasia, Morquio's disease, 938
Dysentery: See also Diarrhea
enterocolitis from Flexner bacillus cured with sulfaguanidine, 504
Dysostosis: See Cranium
Dyspepsia: See Celiac Disease; Gastrointestinal Tract
Dysraphia: See Spina Bifida
Dystonia musculorum deformans, autopsy in case of, 950
Dystrophy, Muscular: See also Atrophy, muscular; etc.
muscular, and muscular shortening (with "webbed" neck); heredofamilial disease, 350
muscular; vitamins E and B_6 in treatment of neuromuscular diseases, 945

Ear: See also Deafness; Hearing; Mastoid; Otorhinolaryngology; etc.
congenital auditory atresia; its plastic repair with functional restoration of hearing and phonation in deaf-mute, 673
Diseases: See Meningitis, otitic; Otitis Media
hereditary syphilis of, 811
plastic correction of protruding ears, 176
Eczema in infancy and childhood, 353
Edema: See also under Brain
hereditary lymphedema (Nonne-Milroy-Meige); report of family with hereditary lymphedema associated with ptosis of eyelid in several generations, 513
physical diagnosis in infancy, 678
Education and Training: See under Children; Schools
Ehlers-Danlos Syndrome: See Joints; Skin, abnormalities
Elbow, fractures of forearm and elbow in children, 189
hemangioma of elbow successfully treated with radium at early age, *785
Electrocardiogram: See under Heart
Electrocoagulation: See under specific headings
Electroencephalography: See under Brain
Embolism: See Thrombosis
Embryology: See Fetus; and under names of special organs and structures
Emesis: See Vomiting
Encephalitis: See also Encephalomyelitis
complicating measles; report of 56 cases with follow-up studies in 32, *265
fatal case following varicella, 668
hemorrhagic; Wernicke's encephalopathy; clinical features and their probable relationship to vitamin B deficiency, 506
periaxialis diffusa; acute hemorrhagic leukoencephalitis; previously undefined entity, 179
tumor of brain simulating, 345
virus hepatitis; contribution to knowledge of clinical picture of poliomyelitis and encephalitis, 819
Encephalography: See Brain, roentgenography
Encephalomyelitis, equine, problem of human transmission of, 948
postinfectious; report of its occurrence following measles and vaccination for smallpox, with complicating bromide poisoning, *585
postvaccinal and measles encephalomyelitis, 940
Endocarditis, subacute bacterial, due to hemolytic streptococci of Lancefield group G, *77
Endocrine Glands: See also Metabolism; and under names of glands
effects of vitamins B_1 and C on endocrine equilibrium in infancy, 805
endocrine factors in acne vulgaris, 514
endocrine problems in adolescence, 510
galactose tolerance test in endocrine disorders in children, *207
Endocrine Therapy: See under names of glands and hormones, as Adrenal Preparations; Pituitary Preparations; Thyroid; etc.
Energy Exchange: See Metabolism
Enteritis: See Colitis; Diarrhea; Dysentery; Gastrointestinal Tract; Intestines, diseases; etc.
Enterobius: See Oxyuriasis
Enterocolitis: See Dysentery
Enuresis: See Urination, incontinence
Enzymes, enzymatic debridement in local treatment of burns; preliminary report, *909
Eosinophils: See also Leukocytes
Loeffler's syndrome, 674
small epidemic of transient pulmonary infiltrations, 811
Epidermis: See Skin
Epilepsy: See also Convulsions; Sclerosis, tuberous
cortical frequency spectrum in, 344
electroencephalography on children, *898
pathologic changes in brains of epileptic persons who died during status epilepticus, 180
Epiloia: See Sclerosis, tuberous
Epinephrine: See Adrenal Preparations
Epiphyses, serous meningitis, ulcerative stomatitis and infectious arthritis with epiphysiolysis of left hip joint in scarlet fever, 491
variations in calcification pattern in epiphyses; their nature and significance, 821
Epituberculosis: See Tuberculosis, pulmonary
Equilibrium, Acid-Base: See Acid-Base Equilibrium
Erysipelas and therapy with sulfonamide compounds, 667
in infancy, *739
periumbilical staphylococcus erysipelas in 20 day old infant, 488
Erythema annulare rheumaticum, prognosis in, 352
multiforme; Stevens-Johnson disease with complete visual recovery, 953
Erythrina, treatment of childhood schizophrenia by metrazol shock modified by B-erythroidin, 949
Erythroblastosis, Fetal: See also Anemia, erythroblastic; Hemopoietic System
acute hemolytic anemia of newborn; preliminary report, *571

Erythrocytes: See Anemia; Blood, cells; Hemoglobin and Hemoglobin Compounds; etc.
Sedimentation: See Blood, sedimentation
Erythroidin: See Erythrina
Escherichia Coli: See Bacteria, coli
Esophagus, abnormalities; brachymegaesophagus with gastric displacement, 818
esophagospasm as cause of scurvy, 806
probable splenic portal thrombosis with roentgenographic study of esophageal varices, 944
Estrogens, absorption of pellets of crystalline testosterone, testosterone propionate, methyl testosterone, progesterone, desoxycorticosterone and stilbestrol implanted in rat, 186
chronic toxicity studies of diethylstilbestrol, 348
effect of estrogens, gonadotropins and growth hormone on mammary glands of hypophysectomized rats, 348
relation of changes in testicular structure induced in rabbit by estrogenic substance to resistance against syphilis, 348
synthetic; clinical experience with some of newer forms, 347
Exanthems: See Communicable Diseases; and under names of exanthematous diseases
Exercise: See Athletics
Exomphalos: See Hernia, umbilical
Expectorants, method for studying expectorant action in animals by direct measurement of output of respiratory tract fluids, 342
Exsiccosis: See Dehydration
Extremities: See also Legs; etc.
abnormalities; congenital malformation of upper and lower extremities in siblings with different fathers, 807
absence; girl born without legs and without arms; report of case, 330
congenital defect of skin in newborn infant, *916
familial occurrence of pruritus, urticaria and paresthesias with hyperkinesis of lower extremities, 823
Paralysis: See also Poliomyelitis
paralysis; obstetric paralysis involving upper and lower limbs, 675
Eyelids: See also Conjunctiva
ptosis, hereditary, and imbecility, 953
ptosis; hereditary lymphedema (Nonne-Milroy-Meige); report of family with hereditary lymphedema associated with ptosis of eyelid in several generations, 513
Eyes: See also Vision; and under names of special structures and diseases
comparative studies on "phacomas" of eyeball and its adnexa; report of cases, 678
Diseases: See Cataract; Ophthalmia; Trachoma; Xerophthalmia; etc.
histologic eye findings in arachnodactyly, 938
muscles; congenital malformations; strands replacing both superior rectus muscles, absence of inferior rectus muscles, microcornea and coloboma of iris; new operative method to correct hypertropia of eyeballs, 822
ophthalmic changes in cystine disease, 512
tuberculosis; allergy studies on tuberculous eyes, 512

Face, Abnormalities: See Harelip
influence of formative dental organs on growth of bones of face, 954
Falkenstein, D.: Acute lymphatic leukemia in childhood, *445
Farber, J. E.: Cushing's syndrome in children; review of literature and report of case, *593
Fat: See also Acid, fatty
in Blood: See Blood, fats and lipoids
in Milk: See under Milk
influence of minor dietary changes on frequency of infant's stools; study of effect of varying content of lactose, milk fat and thiamine, *827
Favism; secondary anemias, 498
Favre-Nicolas Disease: See Lymphogranuloma Venereum
Feces, high incidence of infective stools in small outbreak of infantile paralysis, 488
influence of minor dietary changes on frequency of infants' stools; study of effect of varying content of lactose, milk fat and thiamine, *827
output of bile pigment by newborn infants and by older infants and children, *558
value of complex carbohydrates in diets of normal children, *195
Feeblemindedness: See also Idiocy
hereditary factor in mental deficiency, 181
hereditary ptosis and imbecility, 953
Felty Syndrome: See Splenomegaly
Femur, Epiphyses: See Epiphyses
Fertility: See Reproduction
Fetus: See also Labor; Pregnancy; Umbilical Cord
dependence of fetal growth and storage of calcium and phosphorus on parathyroid function and diet of pregnant rats, 167
effects of morphine on labor, 332
effects of scopolamine on, 332
Injuries: See Newborn Infants
Pathology: See Hydrocephalus
physiology and anatomy of respiratory system in fetus and newborn infant, 486
recording and reproduction (by stethograph) of fetal heart murmur confirmed after birth, 331
transfer of bismuth into fetal circulation after maternal administration of sobisminol, 940
Fever: See also Malaria; Temperature; Typhoid; Typhus; etc.
Cerebrospinal: See Meningitis
influence of hyperpyrexia on ascorbic acid concentration in blood, 485
Rat-Bite: See Rat-Bite Fever
Therapeutic: See under Malaria; etc.
Fibrinogen in Blood: See under Blood
Fibrinolysin: See Blood, fibrin
Fingers and Toes, Abnormalities: See also Arachnodactyly
abnormalities; macrodactylia, 807
abnormalities; symphalangism; familial malformation, *550
Fischer, A. E.: Transitory hemiplegia associated with hypoglycemia in diabetic child with congenital heart disease, *73
Fistula, congenital umbilical fistula or sinus due to persistent omphalomesenteric duct, 505
Fitch, F. R.: Treatment of gonorrheal vulvovaginitis with silver picrate suppositories; report of results in 57 cases, *728
Florman, A. L.: Transitory hemiplegia associated with hypoglycemia in diabetic child with congenital heart disease, *73
Fluids, breast milk secretion during thirst and during forced fluid intake, 805
Fluorescein Method: See Blood, circulation
Fluorides, assimilation of fluorine by rats from natural and synthetic cryolite and from cryolite-sprayed fruits, 937
effect of dietary calcium and phosphorus on assimilation of dietary fluorine, 167
Fluorine: See Fluorides
Food: See also Diet and Dietetics; Nutrition; Vitamins; and under names of various foods, as Bananas; Buttermilk; Fruits and Vegetables; Milk; etc.
allergy; alimentary intolerance simulating subacute infection, 819
Canned: See Canning and Canned Foods
Poisoning: See also Paratyphoid; Salmonella
poisoning; acute diarrheal diseases; outbreak due to Salmonella typhi murium, 177
poisoning; epidemiology of food-borne diseases of gastrointestinal tract, 494
poisoning; treatment of food-borne diseases of gastrointestinal tract, 504
value of complex carbohydrates in diets of normal children, *195
veterinary food inspection, 493

Forearm, fractures of forearm and elbow in children, 189
Foreign Bodies: See also under names of organs and regions
open safety pin, 340
Formol-Gel Test: See Rheumatic Fever
Fossa, Mandibular: See Temporal Bone
Fowler, W. M.: Acute lymphatic leukemia in childhood, *445
Fractures: See under Bones, fragility; Elbow; etc.
Francis Test: See Pneumonia
Frei Reaction: See Lymphogranuloma Venereum
Freud, P.: Symphalangism; familial malformation, *550
Friderichsen-Waterhouse Syndrome: See Adrenals, hemorrhage
Friedreich's Ataxia: See Ataxia, hereditary
Fruits and Vegetables: See also under names of fruits and vegetables, as Bananas; Broccoli; Cauliflower; etc.
assimilation of fluorine by rats from natural and synthetic cryolite and from cryolite-sprayed fruits, 937
comparative costs of vitamin C in fresh and commercially canned fruit and vegetable juices, 171
Fusospirochetosis, renal complications in acute gingivostomatitis in children, 343
Vincent's ulceromembranous gingivostomatitis, 177

Galactose tolerance test in endocrine disorders in children, *207
Gallbladder: See also Bile; Bile Ducts; Biliary Tract
calculi; cholelithiasis in newborn infants, 330
Gallstones: See Gallbladder, calculi
Gastric Juice: See under Stomach
Gastroenteritis: See Gastrointestinal Tract
Gastroenterostomy: See Duodenum, abnormalities
Gastrointestinal Tract: See also Colon; Duodenum; Intestines; Rectum; Stomach; etc.
epidemiology of food-borne diseases of, 494
hereditary hemorrhagic telangiectasia with gastrointestinal bleeding, 503
influence of inositol and other B complex factors on motility of, 329
succinyl sulfathiazole, new bacteriostatic agent locally active in, 177
treatment of food-borne diseases of, 504
veterinary food inspection, 483
Gaucher's Disease: See Anemia, splenic
Gee's Disease: See Celiac Disease
Genitals: See also Urinary Tract; and under names of genitals, as Penis; Testes; Vagina; etc.
reproductive organs in malnutrition, 348
Genitourinary Tract: See Genitals; Urinary Tract; and under organs of genitourinary tract
Germicides: See Sterilization
Gibel, H.: Encephalitis complicating measles; report of 56 cases with follow-up studies in 32, *265
Gingivostomatitis: See Fusospirochetosis
Glands: See under names of glands, as Adrenals; Endocrine Glands; etc.
Globulin in Blood: See Blood, proteins
Therapy: See Measles
Globus, J. H.: Tumors of brain in children and in adolescents; clinical and anatomic survey of 92 verified cases, *604
Glomerulonephritis: See Nephritis
Glycemia: See Blood, sugar
Glycosuria, Renal: See Diabetes, Renal
Gonadotropins: See also Pituitary Preparations
chorionic; antihormone production to crude and purified pregnant mare serum preparations, 186
effect of estrogens, gonadotropins and growth hormone on mammary glands of hypophysectomized rats, 348
Gonadotropins—Continued
reproductive organs in malnutrition, 348
variations in yield of gonadotropic material from green plants in relation to season of growth and *p*H of fresh juice, 347
Gonads: See Endocrine Glands; Genitals; Hermaphroditism; Ovary; Testes
Gonococci, acute gonococcic peritonitis in girl of 9½, 668
Infections: See under Conjunctivitis; Gonorrhea
Gonorrhea: See also under Gonococci
gonorrheal ophthalmia and gonorrheal ophthalmia neonatorum, 951
treatment of gonorrheal vulvovaginitis with silver picrate suppositories; report of results in 57 cases, *728
Gordon, H. H.: Calcium and phosphorus requirements of premature infants, *412
Graham, S. G.: Neonatal mortality, 162
Gravidity: See Pregnancy
Green, W. T.: Second attacks of anterior poliomyelitis; report of 4 cases, *757
Greenwalt, T. J.: Erythroblastosis foetalis (acute hemolytic anemia of newborn); preliminary report, *571
Output of bile pigment by newborn infants and by older infants and children, *558
Grip: See Influenza
Grishman, A.: Newer concepts in diagnosis of congenital heart disease, *922
Growth: See also Diet and Dietetics; Nutrition; etc.
basal heat production in relation to growth; longitudinal study on normal infants 6 to 20 months of age, *1
effect of estrogens, gonadotropins and growth hormone on mammary glands of hypophysectomized rats, 348
effect of pituitary growth substance on development of rats thyroidectomized at birth, 348
need for observations of growth in appraising adequacy of nutrition in childhood, *320
of prematurely born children of school age, 665
relation between development of behavior and pattern of physical growth, 181
studies on growth and development of male children receiving evaporated milk; effect of various vitamin supplements on growth in length and incidence of rickets during first 2 years of life, 168
Guillain-Barré Syndrome: See Nerves, roots
Gustina, F. J.: Cushing's syndrome in children; review of literature and report of case, *593

Haemaphysalis: See Tick Fevers
Haemophilus Pertussis: See Whooping Cough
Hand-Schüller-Christian Disease: See Schüller-Christian Syndrome
Harelip, congenital malformations induced in rats by maternal nutritional deficiency; cleft palate, *882
Harris, C.: Dosage of vitamin D; opinions on vitamin D requirements of infants and children, 158
Head: See Cranium
Hearing: See also Deafness
congenital auditory atresia; its plastic repair with functional restoration of hearing and phonation in deaf-mute, 673
tests; diagnostic significance of audiogram in cases of impaired hearing, 815
Heart: See also Arrhythmia; Blood, circulation; Cardiovascular System; Endocarditis; Myocarditis; Pericarditis; and under names of various conditions, as Rheumatic Fever; etc.
Abnormalities: See also Ductus Arteriosus; Heart, hypertrophy; etc.
abnormalities; congenital heart disease and electrocardiogram, 498
abnormalities; newer concepts in diagnosis of congenital heart disease, *922

Heart—Continued
abnormalities; transitory hemiplegia associated with hypoglycemia in diabetic child with congenital heart disease, *73
athletic activity at puberty wtih reference to cardiac and tuberculous patient, 498
cardiac muscle in poliomyelitis, *733
diagnosis of slight myocardial insufficiency during convalescence from diphtheria, 808
Diseases: See also Endocarditis; Myocarditis; Pericarditis; etc.
Diseases, Congenital: See Heart, abnormalities
diseases; incidence in university student age group, 942
effect of Schaumann's disease on heart and its mechanism, 943
electrocardiographic examinations in scarlet fever, 809
hypertrophy; congenital idiopathic cardiac hypertrophy, *905
hypertrophy: idiopathic cardiac enlargement occurring in infants and children, 174
murmurs; changing heart murmurs of acute rheumatism, 173
murmurs; recording and reproduction (by stethograph) of fetal heart murmur confirmed after birth, 331
rate; paroxysmal tachycardia in 2 month old infant with ventricular rate of 350, *582
Rheumatic Disturbances: See Rheumatic Fever
rupture; case of traumatic rupture of heart valves, 671
tumor, and tuberous sclerosis, 345
Heat: See also Temperature
Production: See Metabolism
stroke; severe type in infancy, 824
Heilman, F. R.: Subacute bacterial endocarditis due to hemolytic streptococci of Lancefield group G, *77
Heine-Medin Disease: See Poliomyelitis
Heliotherapy and Phototherapy: See under names of various organs and diseases
Helium, Bacillus pyocyaneus meningitis following pneumoencephalography, *912
Hell, Dr. J. N., physician of Sopron, introduces smallpox vaccination into Hungary, 668
Helmholz, H. F.: Effects of various urinary antiseptics on strains of Escherichia coli; sulfathiazole; urinary acidity, mandelic acid, methenamine and methenamine mandelate; relative value of sulfathiazole, sulfadiazine, sulfapyridine, sufacetimide and sulfanilamide, *399
Hemangioma, cavernous, of larynx, 672
of elbow successfully treated with radium at early age, *785
roentgen therapy of hemangiomata, 188, 514
Hematology: See Blood; Hemopoietic System
Hematoma, subcortical; surgical treatment, with report of 8 cases, 178
Hemiplegia: See also Extremities, paralysis; Paralysis, obstetric; etc.
transitory, associated with hypoglycemia in diabetic child with congenital heart disease, *73
Hemoglobin and Hemoglobin Compounds: See also Anemia; Blood; etc.
hemoglobin metabolism, 942
Hemolysis: See Anemia, hemolytic; Jaundice, hemolytic
Hemophilia: See also Diathesis, hemorrhagic
hemophilia-like disease in swine, 190
Hemopoietic System, Diseases: See also Anemia; Leukemia; etc.
diseases of blood and hemopoietic organs in infant, 813
Hemorrhage: See also Adrenals, hemorrhage; Blood, coagulation; Encephalitis, hemorrhagic; Hemophilia; Pancreatitis; Purpura haemorrhagica; Retina; Telangiectasis; Tonsillectomy; Umbilicus; etc.
prevention of hemorrhagic diseases of newborn by administration of cow's milk during first 2 days of life, 665
therapy; use of rabbit thrombin as local hemostatic, 941
Hemostasis: See Hemorrhage, therapy
Hepatitis: See Jaundice; Liver, diseases
Hermaphroditism, pseudohermaphroditism, *67
Hernia: See also under Trachea
diaphragmatic; case of traumatic rupture of heart valves, 671
diaphragmatic, congenital (right side), 823
diaphragmatic; diagnosis and treatment, 343
umbilical; exomphalos, 177
umbilical; omphalocele with congenital obstruction; report of case with Meckel's diverticulum, *781
Herter-Gee Disease: See Celiac Disease
Hess, E. R: Infarction of liver and hypoprothrombinemia; report of their association in newborn infant with failure of vitamin K therapy, *258
Heymann, W.: Independence of serum cholesterol from exogenous cholesterol in infants and in children, *235
Hirschsprung's Disease: See Colon, dilatation
Histone Zinc Insulin: See Diabetes Mellitus
Hodge, G. B.: Enzymatic débridement in local treatment of burns; preliminary report, *909
Hodges, R. G.: Serum cholesterol values for infants and children, *858
Holland, M.: Large cyst of omentum; its occurrence in 3 year old child, *920
Hormones: See Adrenal Preparations; Endocrine Glands; and under names of organs, as Pituitary Body; Thymus; etc.
Gonadotropic: See Gonadotropins
Sex: See Androgens; Estrogens; Pituitary Preparations; and under names of organs, as Pituitary Body; etc.
Thyrotropic: See Pituitary Preparations
Hospitals, compulsory hospitalization of scarlet fever patients, 809
prevention of congenital syphilis in large urban hospital; study of clinic administration, 339
Howell, K. M.: Studies in immunity to pertussis; effect of stimulating dose of Haemophilus pertussis vaccine, *730
Hubbard, J. P.: Paroxysmal tachycardia in 2 month old infant with ventricular rate of 350, *582
Hummel, F. C.: Value of complex carbohydrates in diets of normal children, *195
Hydrocephalus, lacunar skull due to pressure, 511
otorhinogenic, 345
Hydrogen Ion Concentration: See Acid-Base Equilibrium; Acidosis; etc.
Hydroxyethylapocupreine: See Pneumococci
Hypercholesteremia: See Blood, cholesterol
Hyperelasticity: See Skin, abnormalities
Hypergenitalism: See under Adolescence
Hyperglycemia: See Blood, sugar
Hyperkinesis: See Movements
Hyperlipemia: See Blood, fats and lipoids
Hyperpyrexia: See Fever
Hypertelorism, ocular, of Greig, 806
Hypertension: See Blood pressure, high
Hyperthermia: See Fever
Hyperthyroidism: See under Thyroid
Hypertrophy: See Acromegaly; and under names of organs and regions, as Heart; Liver; etc.
Hypochloremia: See Blood, chlorides
Hypogenitalism: See Genitals; Pituitary Body
Hypoglycemia: See Blood, sugar; Diabetes Mellitus
Hypophysectomy: See Pituitary Body
Hypophysis: See Pituitary Body
Hypoprothrombinemia: See Blood, prothrombin
Hypothyroidism: See under Thyroid
Hysteria, pediatric aspects of Salem witchcraft tragedy; lesson in mental health, *788

Ichthyosis congenita; characteristic case beginning as lamellous exfoliation and without malformations, 515
Icterus: See Jaundice
Idiocy: See also Feeblemindedness
congenital form of amaurotic family idiocy, 183
Mongolian: See Mongolism

Ileus: See Intestines
Iliff, A.: Basal metabolism of normal boys and girls from 2 to 12 years old, inclusive; report of further study, *834
Basal metabolism of normal children from 13 to 15 years old, inclusive, *845
Imbecility: See Feeblemindedness; Idiocy
Immunity: See also under Anaphylaxis and Allergy; Diphtheria; Streptococci; Tuberculosis; etc.
discussion on active immunization; some present-day problems, 337
Impetigo contagiosa, bacteriology of, 353
Inanition: See Nutrition
Industry, breast feeding in relation to female labor as it affects Birmingham, 147
Infant Feeding: See also Diet and Dietetics; Nutrition; Vitamins; and under names of various foods, as Milk; etc.
breast feeding in relation to female labor as it affects Birmingham, 147
calorie requirements of full-term and premature infants in neonatal period; formula; its uses and limitations, 487
diet in second and third periods of infancy, 169
feeding with citric acid milk, 805
influence of diet of newborn infant on prothrombin index, 487
influence of minor dietary changes on frequency of infants' stools; study of effect of varying content of lactose, milk fat and thiamine, *827
intake of amino acids by breast milk fed infants and amino acid composition of cow's milk and human milk, 168
is boiled breast milk to be regarded as appropriate infant's food? 805
prevention of hemorrhagic disease of newborn by administration of cow's milk during first 2 days of life, 665
skim milk acidified with lactic or citric acid as adjuvant to buttermilk, 170
studies on growth and development of male children receiving evaporated milk; effect of various vitamin supplements on growth in length and incidence of rickets during first 2 years of life, 168
weight of healthy breast-fed infants during first year of life, 664
Infant Mortality: See also Newborn Infants; Premature Infants; Stillbirths
and prematurity, 665
high stillbirth and neonatal mortality, 938
in Santos; its causes and ways to offset them, 664
need of widespread feminine cooperation in fight against, 486
neonatal mortality, 162
Infant Welfare: See also Child Welfare
need of widespread feminine cooperation in fight against infant mortality, 486
Infantile Paralysis: See Poliomyelitis
Infantilism, Intestinal: See Celiac Disease
Renal: See Dwarfism
Splenic: See Splenomegaly
Infants: See also Children; Infant Feeding; Infant Mortality; Infant Welfare; Newborn Infants; Pediatrics; Premature Infants; etc.
Diseases: See under names of various diseases
Growth: See Growth
values of plasma phosphatase and blood phosphorus in healthy children born at term and in premature children, 499
Infarction: See under Liver
Infection: See also Immunity; Septicemia; and under names of bacteria, organs and regions
alimentary intolerance simulating subacute infection, 819
serum cholesterol values for infants and children, *858
Infectious Diseases: See Communicable Diseases; Diphtheria; Infection; Pneumococci; Typhoid; etc.
Influenza, complement fixation with embryo fluid as antigen, 338
epidemic of influenza B occurring in group of rheumatic children concurrent with outbreak of streptococcal pharyngitis; clinical and epidemiologic observations, 807
grip meningitis, 180
influenzal meningitis and its treatment, 811
influenzal meningitis; case report, 345
influenzal meningitis; successful treatment of case in infant, 346
resistance of virus to drying and its demonstration on dust, 937
suppurative pericarditis due to Haemophilus influenzae type B; characteristic syndrome ushered in by symptoms of croup, *305
tracheobronchitis complicating grip and its treatment, 817
Injections: See Blood, transfusion; etc.
Injuries: See under Newborn Infants; and under names of organs and regions, as Nose; etc.
Inositol, influence of inositol and other B complex factors on motility of gastrointestinal tract, 329
Insects: See Mosquitoes
Insensible Perspiration: See Metabolism
Instruments: See also Apparatus
effect of noise on normal and impaired hearing, 816
sterilization of syringes and needles, 337
Insulin: See Pancreas
Internal Secretions: See Endocrine Glands
Intestines: See also Colon; Duodenum; Gastrointestinal Tract; Rectum
Diseases: See also Diarrhea; Dysentery; etc.
diseases; discussion on active immunization of enteric fever; some present-day problems, 337
diseases; laboratory aids in diagnosis and control of enteric disease, 504
Intussusception: See Intussusception
omphalocele with congenital obstruction; report of case with Meckel's diverticulum, *781
Parasites: See Dysentery
persisting vitelline remnants (umbilical cyst and Meckel's diverticulum), 344
volvulus in newborn infant, 820
Intussusception, acute, 343
treatment of, 177
Inulin, relation of high and low urea clearances to inulin and creatinine clearances in children with nephrotic syndrome, 949
Iodine and Iodine Compounds, effect of administering thyrotropic hormone with and without iodine on thyroid tissue metabolism, 186
Iris, abnormalities; congenital malformations; strands replacing both superior rectus muscles, absence of inferior rectus muscles, microcornea and coloboma of iris; new operative method to correct hypertropia of eyeballs, 822

Janney, F. R.: Sulfadiazine; review of its use in treatment of children, *702
Janota, M.: Studies in immunity to pertussis; effect of stimulating dose of Haemophilus pertussis vaccine, *730
Jaundice, acute hemolytic anemia in case of acute hepatitis, 814
biopsy of liver in cases with intermittent juvenile jaundice, 821
Parrot's disease with icterus and umbilical hemorrhage, 670
Jaws, hypoplasia of mandible; report of case, with résumé of literature and suggestions for modified form of treatment, *440
Jejunum: See Intestines
Jenner, Edward, history of smallpox inoculation before, 491
Jervis, G. A.: Guillain-Barré syndrome ("infectious polyneuritis") and acute anterior poliomyelitis, *431
Johnson-Stevens Disease: See Erythema multiforme

Joints: See also under names of individual joints
acute rheumatism and trauma, 173
Diseases: See Arthritis; etc.
syndrome of cutaneous fragility and hyperelasticity and articular hyperlaxity, *247
Josephs, H. W.: Studies on vitamin A; vitamin A and total lipid of serum in pneumonia, *712
Jost, H.: Diagnosis of juvenile psychosis, *868

Kahn Test: See Syphilis
Kaplan, I. I.: Hemangioma of elbow successfully treated with radium at early age, *785
Kaplan, L.: Infarction of liver and hypoprothrombinemia; report of their association in newborn infant with failure of vitamin K therapy, *258
Kean, B. H.: Waterhouse-Friderichsen syndrome on Isthmus of Panama, *426
Keith, H. M.: Subacute bacterial endocarditis due to hemolytic streptococci of Lancefield group G, *77
Kelly, M.: Respiratory metabolism in infancy and in childhood; regulation of body temperature of premature infants, *376
Kenny Treatment: See Poliomyelitis
Keratitis: See Keratoconjunctivitis
Keratoconjunctivitis; keratoconjunctival lesions observed at high altitudes in Bolivia, 951
Keratoderma: See Ichthyosis
Kerman, W. Z.: Bacillus pyocyaneus meningitis following pneumoencephalography, *912
Kernicterus: See under Jaundice
Keto Steroids: See Urine, steroids
Kidneys: See also Urinary Tract
abnormalities; case of congenital bilateral renal hypoplasia with short review of literature, 184
acid-base balance, renal function and gastric secretion during hypochloremia in dog, 803
blood supply; studies in experimental hypertension, 174
calculi, etiology and diagnosis of, 185
Carbuncle: See Nephritis
Diseases: See also under Nephritis
diseases; lipid nephrosis; observations over period of 20 years, *355
diseases; pneumococcic sepsis and peritonitis in child suffering from nephrosis cured with sulfapyridine, 510
diseases; total and fractional blood lipid levels in nephrotic syndrome, *770
influence of pregnancy on renal cortex of mice as indicated by structure of Bowman's capsule, 348
relation of high and low urea clearances to inulin and creatinine clearances in children with nephrotic syndrome, 949
renal excretion of inorganic phosphate in relation to action of vitamin D and parathyroid hormone, 484
structure of Bowman's capsule in castrate and testosterone-treated male mice as index of hormonal effects on renal cortex, 348
toxicity of orally administered potassium salts in renal insufficiency, 509
tuberculosis; interval between renal tuberculosis and initial tuberculosis, 671
Koch's Bacillus: See Tuberculosis
Kohn, J. L.: Lipid nephrosis; observations over period of 20 years, *355
Kresky, P. J.: Suppurative pericarditis due to Haemophilus influenzae type B; characteristic syndrome ushered in by symptoms of croup, *305

Labor: See also Placenta; Pregnancy; etc.
Complications: See also Fetus; Newborn Infants; etc.
effects of morphine on, 332
Laboratory aids in diagnosis and control of enteric disease, 504
Lactation: See also Colostrum; Infant Feeding; Milk
and uterine distention, 183
artificial stimulation in primitive cultures, 481
Lactation—Continued
assay of posterior pituitary factors which contract lactating mammary gland, 349
breast feeding in relation to female labor as it affects Birmingham, 147
breast milk secretion during thirst and during forced fluid intake, 805
dietary requirements for fertility and lactation, 937
does pregnancy suppress lactogenic hormone of pituitary? 187
Lactose, influence of minor dietary changes on frequency of infants' stools; study of effect of varying content of lactose, milk fat and thiamine, *827
Landes, J. H.: Reactions from diphtheria toxoid, *519
Landry's Paralysis: See Paralysis, acute ascending
Lard, nutritive properties of steam-rendered lard and hydrogenated cottonseed oil, 167
Laryngitis: See under Larynx
Laryngotracheobronchitis: See Respiratory Tract, diseases
Larynx, cavernous hemangioma of, 672
congenital cyst of, 176
ulcerative laryngitis as complication of measles, 808
Leach, W.: Large cyst of omentum; its occurrence in 3 year old child, *920
Lead, choked disks in lead encephalopathy, 945
poisoning; tuberous sclerosis, 345
Lederer's Anemia: See Anemia, hemolytic
Legs: See also Extremities
blood supply; congenital arteriovenous anastomosis, 340
Lens, Crystalline, Opacity: See Cataract
Leukemia: See also Chloroma
diseases of blood and hemopoietic organs in infant, 813
lymphatic, acute, in childhood, *445
monocytic and myeloid-leukemoid reaction in severe fibrinous-necrotic stomatitis of child, 505
Leukocytes: See also under Blood; Eosinophils; Leukemia; Mononucleosis, Infectious; etc.
influence of tonsillectomy on blood picture, 815
toxic reaction to sulfapyridine, 954
Leukoencephalitis: See Encephalitis periaxialis diffusa
Levinson, A.: Bacillus pyocyaneus meningitis following pneumoencephalography, *912
Levulose in Urine: See under Urine
Lewis, R. C.: Basal metabolism of normal boys and girls from 2 to 12 years old, inclusive; report of further study, *834
Basal metabolism of normal children from 13 to 15 years old, inclusive, *845
Lichty, J. A., Jr.: Streptococcic antifibrinolysin in newborn infants; true and false tests, *60
Limbs: See Extremities; Legs
Lipemia: See Blood, fats and lipoids
Lipid Nephrosis: See Kidneys, diseases
Lipogranulomatosis: See Schüller-Christian Syndrome
Lipoidosis: See Anemia, splenic; Idiocy; Schüller-Christian Syndrome
Lipoids, in Blood: See Blood, fats and lipoids
Lips, Harelip: See Harelip
Lithiasis: See under Bladder; Gallbladder, calculi; Kidneys, calculi; etc.
Litvak, A. M.: Encephalitis complicating measles; report of 56 cases with follow-up studies in 32, *265
Liver: See also Biliary Tract
biopsy in cases with intermittent juvenile jaundice, 821
cirrhosis; serum cholesterol values for infants and children, *858
clearance of bilirubin from plasma; measure of excreting power of liver, 804
diseases; virus hepatitis; contribution to knowledge of clinical picture of poliomyelitis and encephalitis, 819
hypertrophy; enlargement of liver in diabetic children, 821

Liver—Continued
infarction and hypoprothrombinemia; report of their association in newborn infant with failure of vitamin K therapy, *258
new test for hepatic insufficiency, 819
Oils: See Cod Liver Oil
production of cytoplasmic inclusions in liver cells of rats injected with certain proteins, 190
Therapy: See Anemia
vitamin K in other than hemorrhagic diseases, 339
Llewellyn, J. S.: Hypoplasia of mandible; report of case, with résumé of literature and suggestions for modified form of treatment, *440
Loeffler's Syndrome: See Eosinophils; Lungs, pathology; Tuberculosis, pulmonary
Lourie, R. S.: Rate of secretion of parotid glands in normal children; measurement of function of autonomic nervous system, *455
Low, N. L.: Electroencephalography on children, *898
Lucchesi, P. F.: Cardiac muscle in poliomyelitis, *733
Lues: See Syphilis
Lungs: See also Respiration; Respiratory Tract; Thorax; etc.
agenesis, 817
agenesis in infant, *776
Collapse: See also Pneumothorax
collapse; atelectasis and bronchiectasis; experimental study concerning their relationship, 816
Diseases: See Tuberculosis, pulmonary; etc.
method of treatment of large pulmonary air cysts (balloon cysts) by endocutaneous flap, 816
pathology; Loeffler's syndrome, 674
pseudocaverns, 817
small epidemic of transient pulmonary infiltrations, 811
Tuberculosis: See Tuberculosis, pulmonary
Lymph Nodes: See Leukemia, lymphatic; Mononucleosis, Infectious
Lymphedema: See Edema
Lymphocytes: See under Choriomeningitis
Lymphogranuloma, Inguinale: See Lymphogranuloma Venereum
Schaumann's: See Sarcoidosis
Lymphogranuloma Venereum in children, 812
Lymphoid Tissues: See Adenoids; Nasopharynx; Tonsils; etc.
Lyon, R. A.: Causes of prematurity; influence of race and sex on duration of gestation and weight at birth, *523

McCune, D. J.: Intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome); report of case in which increased urinary organic acids were detected and identified, with review of literature, *81
Mackay, H.: Dosage of vitamin D; opinions on vitamin D requirements of infants and children, 158
MacLachlan, E. A.: Excretion of 17-keto steroids by normal and by abnormal children, *364
McNeil, S.: Neonatal mortality, 162
Macrodactylia: See Fingers and Toes, abnormalities
Macy, I. G.: Value of complex carbohydrates in diets of normal children, *195
Magnesium balance studies with infants, 167
Malaria, accidental transmission (following transfusion), 172
complications in central nervous system in malaria, 495
Therapeutic: See under Poliomyelitis
Malformations: See Abnormalities and Deformities; and under names of organs and regions
Malnutrition: See under Dystrophy; Nutrition
Mammary Gland: See Breast
Mammogen: See Pituitary Body
Mandible: See Jaws
Mantoux Test: See under Tuberculosis
Manzullo Test: See under Diphtheria
Marble Bones: See Osteosclerosis fragilis
Marfan's Syndrome: See Arachnodactyly
Marples, E.: Calcium and phosphorus requirements of premature infants, *412
Masculinization: See Hermaphroditism
Mason, H. H.: Intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome); report of case in which increased urinary organic acids were detected and identified, with review of literature, *81
Mastoid, acutely involved mastoid (without complications) before and after operation: clinical and roentgenologic study, 175
radiologic study, 499
surgery; indications for operation on ear in infancy, 500
Mastoiditis: See also Otitis Media
acute catarrhal, 943
and sedimentation test, 815
pathologic aspects of, 501
Maternity: See also Labor; Pregnancy
Subcommittee on Maternity and Child Care, 680
Measles, encephalitis complicating measles; report of 56 cases with follow-up studies in 32, *265
human cord serum globulin in modification and prevention of, 334
postinfectious encephalomyelitis; report of its occurrence following measles and vaccination for smallpox, with complicating bromide poisoning, *585
postvaccinal and measles encephalomyelitis, 940
ulcerative laryngitis as complication of, 808
Meckel's Diverticulum: See under Intestines
Mediastinum; syphilitic mediastinitis in infant of 2 months, 672
Medicine: See also Surgery; etc.
military; dosage interval in sulfapyridine administration, 955
Medin-Heine Disease: See Poliomyelitis
Mediterranean Anemia: See Anemia, erythroblastic
Megacolon: See Colon, dilatation
Meige-Milroy-Nonne Disease: See Edema
Melorheostosis: See Osteosclerosis
Menarche: See Menstruation
Meningitis: See also Choriomeningitis; Meningococci
and septicemia of staphylococcic origin, 668
Bacillus pyocyaneus meningitis following pneumoencephalography, *912
cerebrospinal, of nurslings cured by exclusive use of sulfanilamide, 666
chemotherapy of meningococcic cerebrospinal meningitis, 667
grip meningitis, 180
influenzal, and its treatment, 811
influenzal; case report, 345
influenzal; successful treatment of case in infant, 346
otitic; indications for surgical treatment and use of sulfonamide compounds, 947
otogenic, pathology and treatment, 948
pneumococcal; recovery, 346
pneumococcic, treatment of, 945
serous, as complication of scarlet fever, 810
serous, ulcerative stomatitis and infectious arthritis with epiphysiolysis of left hip joint in scarlet fever, 491
therapy of cerebrospinal fever; comparative analysis of therapeutic results in 97 cases from Charity Hospital of Louisiana at New Orleans, 940
Meningococci: See also Meningitis
chemotherapy of meningococcic cerebrospinal meningitis, 667
meningococcemia without meningitis, 489
Menorrhagia: See under Menstruation
Menstruation, attempts to induce menstruation by operative ischemia in monkeys, 183
menstrual abnormalities of adolescence, 509
premenstrual state in young girls, *296
Mental Diseases: See Feeblemindedness; Mental Hygiene; Nervous and Mental Disabilities; Psychiatry; etc.

Mental Hygiene, pediatric aspects of Salem witchcraft tragedy; lesson in mental health, *788
Mercury, absorption of externally applied ammoniated mercury, 352
Mesentery, giant angioma of, 178
intermittent vomiting following constriction of duodenum by mesenteric pedicle, 818
Metabolism: See also under specific headings, as Carbohydrates, metabolism; etc.
basal heat production in relation to growth; longitudinal study on normal infants 6 to 20 months of age, *1
basal, of normal boys and girls from 2 to 12 years old, inclusive; report of further study, *834
basal, of normal children from 13 to 15 years old, inclusive, *845
developmental changes in attitude as 1 factor determining energy output in motor performance, 181
magnesium balance studies with infants, 167
respiratory metabolism in infancy and in childhood; regulation of body temperature of premature infants, *376
standard metabolism of adolescence, 481
Methenamine, effects of various urinary antiseptics on strains of Escherichia coli; sulfathiazole; urinary acidity, mandelic acid, methenamine and methenamine mandelate; relative value of sulfathiazole, sulfadiazine, sulfapyridine, sulfacetimide and sulfanilamide, *399
Microcornea: See Cornea, abnormalities
Micturition: See Urination
Midget: See Dwarfism
Milk: See also Buttermilk; Infant Feeding
determination of soybean milk used as adulterant in cow's milk, 170
feeding of infants with citric acid milk, 805
Human: See also Infant Feeding; Lactation
human, ascorbic acid content of, 806
human; is boiled breast milk to be regarded as appropriate infant's food? 805
influence of minor dietary changes on frequency of infants' stools; study of effect of varying content of lactose, milk fat and thiamine, *827
intake of amino acids by breast milk fed infants and amino acid composition of cow's milk and human milk, 168
skim milk acidified with lactic or citric acid as adjuvant to buttermilk, 170
studies on growth and development of male children receiving evaporated milk; effect of various vitamin supplements on growth in length and incidence of rickets during first 2 years of life, 168
Milroy-Nonne-Meige Disease: See Edema
Mitosis: See Cells, division
Moeller-Barlow's Disease: See Scurvy
Molluscum contagiosum corneae, 515
Moncrieff, A.: Neonatal mortality, 162
Mongolism, biology and physical chemistry of, 949
Monocytes: See Mononucleosis, Infectious; etc.
Mononucleosis, Infectious, 813
Moore, L. V.: Nutrition as conditioning factor in rheumatic state, *744
Morphine: See Anesthesia
Morquio's Disease: See Bones, atrophy; Dyschondroplasia
Morris, N.: Dosage of vitamin D; opinions on vitamin D requirements of infants and children, 158
Morrison, H. J.: Omphalocele with congenital obstruction; report of case with Meckel's diverticulum, *781
Mortality Statistics: See Infant Mortality; Newborn Infants; etc.
Mosquitoes: See also Malaria
tularemia caused by insect bite, 670
Mouth: See Stomatitis; etc.
Movements: See also Muscles
familial occurrence of pruritus, urticaria and paresthesias with hyperkinesis of lower extremities, 823
Moving Pictures, children's reactions to movie horrors and radio crime, 182
Mumps: See Parotitis
Murmurs: See Heart, murmurs
Muscles, Atrophy: See Atrophy, muscular
contractions; disuse atrophy of skeletal muscles, 187
Dystrophy: See Dystrophy, muscular
muscular shortening and dystrophy (with "webbed" neck); heredofamilial disease, 350
Paralysis: See Paralysis
Tonus: See Dystonia
Myasthenia, generalized muscular weakness as toxic reaction to digitalis, 515
Mycobacteria: See Tuberculosis
Myeloma, multiple, in child of 8 years, 950
Myelomeningocele: See Spina Bifida
Myelosis: See Bones, marrow
Myocarditis, cardiac muscle in poliomyelitis, *733
interstitial, in mice and rats produced by neoprontosil, sulfanilamide, sodium sulfapyridine and sodium sulfathiazole, 175
Myocardium: See Heart; Myocarditis
Myxedema, Congenital: See Cretinism

Nanism: See Dwarfism
Naphthoquinone: See Vitamins, K
Nasopharynx, relation of nasopharyngitis to ulcerative colitis, 503
Neale, A. V.: Reports of Subcommittees of British Paediatric Association, 147
Neck, abnormalities; muscular shortening and dystrophy (with "webbed" neck); heredofamilial disease, 350
glandular cysts, 511
Needles, sterilization of syringes and needles, 337
Negroes, causes of prematurity; influence of race and sex on duration of gestation and weight at birth, *523
Nelson, N. B.: Second attacks of anterior poliomyelitis; report of 4 cases, *757
Nelson, R. C.: Congenital malformations induced in rats by maternal nutritional deficiency; cleft palate, *882
Nematodes: See Oxyuriasis; etc.
Neoarsphenamine: See Syphilis
Neoplasms: See Sarcoma; etc.
Neoprontosil: See Streptococci
Nephrectomy: See under Kidneys
Nephritis: See also Kidneys
acute, allergic pathogenesis of, 949
renal complications in acute gingivostomatitis in children, 343
Nephrosis: See Kidneys, diseases; Nephritis
Nerves: See also Nervous System; Neuritis; Paralysis
Optic: See also Neuritis, optic
optic, aplasia of, 951
optic; coloboma in human embryo, 512
optic; hereditary optic atrophy with dominant transmission and early onset, 351
optic; marble bones and optic atrophy, 950
roots; Guillain-Barré syndrome ("infectious polyneuritis") and acute anterior poliomyelitis, *431
Nervous and Mental Disabilities: See also Chorea; Dementia Praecox; Encephalitis; Feeblemindedness; Idiocy; Psychoanalysis; etc.
children's reactions to movie horrors and radio crime, 182
diagnosis of juvenile psychosis, *868
enuresis, 510
important factor in eating disturbances of childhood, 346
Nervous System: See also Brain; Nerves; Reflex; Spinal Cord; etc.
complications in central nervous system in malaria, 495
Diseases: See also Epilepsy; Neuritis; etc.
diseases; neurotropic virus diseases of man, 493

Nervous System—Continued
pathologic changes in brains of epileptic persons who died during status epilepticus, 180
rate of secretion of parotid glands in normal children; measurement of function of autonomic nervous system, *455
Neuritis, optic; choked disks in lead encephalopathy, 945
Neurofibromatosis; Recklinghausen's disease in child 3½ years old, 953
Neurohypophysis: See Pituitary Body
Neuroses and Psychoneuroses: See Nervous and Mental Disabilities
Neutrophils: See Leukocytes
Nevi, Vascular: See Angioma
Neville, R. L.: Omphalocele with congenital obstruction; report of case with Meckel's diverticulum, *781
Newborn Infants: See also under names of diseases, as Anemia; Conjunctivitis; Erysipelas; Impetigo; Jaundice; Meningitis; Syphilis; Tetany; etc.
blood prothrombin in, 331
calcium therapy in control of intracranial pressure with reference to, 331
calorie requirements of full-term and premature infants in neonatal period; formula; its uses and limitations, 487
cholelithiasis in, 330
congenital defect of skin in, *916
costal osteomyelitis with pneumothorax in, 665
effect of depriving infant of its placental blood, 939
erythroblastosis foetalis (acute hemolytic anemia of newborn); preliminary report, *571
hypoplasia of mandible; report of case, with résumé of literature and suggestions for modified form of treatment, *440
infarction of liver and hypoprothrombinemia; report of their association in newborn infant with failure of vitamin K therapy, *258
influence of diet on prothrombin index, 487
K avitaminosis as cause of hemorrhagic diathesis in newborn and older infants, 332
neonatal pneumothorax, 332
output of bile pigment by newborn infants and by older infants and children, *558
physiology and anatomy of respiratory system in fetus and newborn infant, 486
prevention of hemorrhagic disease of newborn by administration of cow's milk during first 2 days of life, 665
prevention of hypoprothrombinemia by treating pregnant woman with vitamin K, 333
prothrombin in; further observations on prothrombin response to intravenous administration of water-soluble naphthoquinone, 487
retinal hemorrhages in, 330
some problems of; preliminary report, 666
streptococcic antifibrinolysin in; true and false tests, *60
volvulus in, 820
Nicolas-Favre Disease: See Lymphogranuloma Venereum
Nicotinic Acid: See also Vitamins, B
and aphthous stomatitis, 945
Nipple: See Breast
Nodes: See Rheumatic Fever; etc.
Noise, effect on normal and impaired hearing, 816
Nomenclature, deaf-mutism, 501
Nonne-Milroy-Meige Disease: See Edema
Nose: See also Nasopharynx; Otorhinolaryngology; etc.
congenital atresia of posterior choanae of nasal fossae, 341
injuries in children; diagnosis and treatment, 353
Nutrition: See also Diet and Dietetics; Dystrophy; Food; Infant Feeding; Metabolism; Vitamins; etc.
as conditioning factor in rheumatic state, *744
blood sugar curves in chronic nutritional disturbances, 804
Nutrition—Continued
complementary power of blood serum in nutritional disturbances of infants, 804
congenital malformations induced in rats by maternal nutritional deficiency; cleft palate, *882
genuine tetanic nutritional cataract, 953
need for observations of growth in appraising adequacy of nutrition in childhood, *320
reproductive organs in malnutrition, 348

Oak poisoning; cause removing treatment, 189
Obesity: See also Pituitary Body
excretion of 17-keto steroids by normal and by abnormal children, *364
in relation to puberty, 482
what to do about fat child at puberty, 482

OBITUARIES:
Stern, Henry S., 327

Obstetric Injuries: See under Extremities; Newborn Infants
Obstetrics: See Hospitals; Labor; Maternity; Pregnancy; etc.
Obstruction: See under Duodenum; Intestines; Ureters; etc.
Oil: See also Cod Liver Oil; Fat; etc.
effect of certain fats and unsaturated fatty acids on utilization of carotene, 167
nutritive properties of steam-rendered lard and hydrogenated cottonseed oil, 167
Olcott, C. T.: Agenesis of lung in infant, *776
Old Age, thiamine and pyrimidine studies on older subjects, 330
Omentum, large cyst; its occurrence in 3 year old child, *920
Omphalocele: See Hernia, umbilical
Omphalomesenteric Duct: See Vitelline Duct
Ophthalmia: See also Conjunctivitis
Gonorrheal: See Gonorrhea
neonatorum, gonorrheal, and gonorrheal ophthalmia, 951
Ornithosis: See Psittacosis
Orthodontia: See under Teeth
Orthopedics: See under Bones; Poliomyelitis; etc.
Orthoptics: See Strabismus
Osler's Disease: See Telangiectasis
Ossification: See Bones, growth
Osteochondrodystrophy: See Dyschondroplasia
Osteogenesis Imperfecta: See Bones, fragility
Osteomalacia, calcium and phosphorus metabolism in; pathogenetic role of pregnancy and relative importance of calcium and vitamin D supply, 511
Osteomyelitis, acute hematogenous, 510
costal, with pneumothorax in newborn infant, 665
presternal staphylococcic abscess complicating osteomyelitis, 676
Osteopetrosis: See Osteosclerosis fragilis
Osteopsathyrosis: See Bones, fragility
Osteosclerosis fragilis; marble bones and optic atrophy, 950
Otitis Media: See also Mastoiditis
abscess of mandibular fossa secondary to, 176
otitic meningitis; indications for surgical treatment and use of sulfonamide compounds, 947
otogenous tetanus, 810
pathology and treatment of otogenic meningitis in childhood, 948
Otorhinolaryngology, use of sulfonamide compounds in otorhinology, 944
Ovary, effect of increasing number of daily injections of gonadotropic preparations on ovaries of immature rats, 185
Oxygen: See also Respiration
intravenous administration of, 955
Oxyuriasis, studies on; summary and conclusions, *46

Palate, cleft, and mechanism of speech, 341
cleft; congenital malformations induced in rats by maternal nutritional deficiency, *882
Palsy: See Paralysis

Panama, Waterhouse-Friderichsen syndrome on Isthmus of Panama, *426
Pancreatitis, acute, diabetic coma and Bacillus welchii peritonitis, *36
acute hemorrhagic, in 6 year old child, 674
Pannus: See Trachoma
Papain, enzymatic débridement in local treatment of burns; preliminary report, *909
Papilledema: See Neuritis, optic
Paralysis: See also Extremities, paralysis; Hemiplegia; Poliomyelitis; etc.
acute ascending; changes in spinal cord in Landry's paralysis, 675
Birth: See Paralysis, obstetric
Bulbar: See Poliomyelitis
cerebral palsy problem, 945
Infantile: See Poliomyelitis
obstetric, involving upper and lower limbs, 675
Periodic: See Extremities, paralysis
rehabilitation of cerebral palsy, 179
Paraplegia: See Extremities, paralysis
Parasites: See under names of parasitic diseases, as Oxyuriasis; etc.
Parathyroid, dependence of fetal growth and storage of calcium and phosphorus on parathyroid function and diet of pregnant rats, 167
Paratyphoid and typhoid in nurslings, 669
Paresthesias: See Sensation, disorders
Parotid Gland, rate of secretion of parotid glands in normal children; measurement of function of autonomic nervous system, *455
Parotitis, peritonitis due to perforation of biliary vesicle in course of typhoid fever accompanied by suppurative parotitis, 811
Parrot's Disease: See Pseudoparalysis
Parturition: See Labor
Patch Test: See Anaphylaxis and Allergy
Paul-Bunnell Test: See Mononucleosis, Infectious
Peale, A. R.: Cardiac muscle in poliomyelitis, *733
Pediatric societies, directory of, 959
Pediatrics: See also Children; Hospitals; Newborn Infants; and under names of specific diseases
pediatric aspects of Salem witchcraft tragedy; lesson in mental health, *788
pediatrician and intellectual culture, 513
posology in, 191
Penis, primary and secondary sexual characteristics; study of their development in males from birth through maturity, with biometric study of penis and testes, *535
Peptic Ulcer, surgery in peptic ulceration of stomach and duodenum in infants and children, 342
Periarteritis nodosa, 811
Pericarditis, suppurative, due to Haemophilus influenzae type B; characteristic syndrome ushered in by symptoms of croup, *305
Peritonitis, acute gonococcic, in girl of 9½, 668
diabetic coma, acute pancreatitis and Bacillus welchii peritonitis, *36
due to perforation of biliary vesicle in course of typhoid fever accompanied by suppurative parotitis, 811
pneumococcic sepsis and peritonitis in child suffering from nephrosis cured with sulfapyridine, 510
vomiting from postoperative inflammatory reaction in infancy, 817
Perlstein, M. A.: Bacillus pyocyaneus meningitis following pneumoencephalography, *912
Infarction of liver and hypoprothrombinemia; report of their association in newborn infant with failure of vitamin K therapy, *258
Perspiration, Insensible: See Metabolism
Pertussis: See Whooping Cough
Peshkin, M. M.: Immunity to tetanus induced by third dose of toxoid 2 years after basic immunization, based on study of 31 allergic children, *873
Petrous Bone: See under Temporal Bone
Pfeiffer's Bacillus: See Influenza
Phacoma, comparative studies on "phacomas" of eyeball and its adnexa; report of cases, 678
Phagocytes and Phagocytosis: See Immunity; Leukocytes
Pharynx: See also Nasopharynx
epidemic of influenza B occurring in group of rheumatic children concurrent with outbreak of streptococcal pharyngitis; clinical and epidemiologic observations, 807
Phenytoin, effects of sodium diphenyl hydantoinate (dilantin) on blood ascorbic acid level in guinea pigs, 170
Phonation: See Speech
Phosphatase in Blood: See Blood, phosphatase
Phosphate: See Phosphorus and Phosphorus Compounds
Phosphorus and Phosphorus Compounds; calcium and phosphorus metabolism in osteomalacia; pathogenetic role of pregnancy and relative importance of calcium and vitamin D supply, 511
calcium and phosphorus requirements of premature infants, *412
dependence of fetal growth and storage of calcium and phosphorus on parathyroid function and diet of pregnant rats, 167
effect of dietary calcium and phosphorus on assimilation of dietary fluorine, 167
in Blood: See Blood, phosphorus
renal excretion of inorganic phosphate in relation to action of vitamin D and parathyroid hormone, 484
studies of calcium and phosphorus metabolism; influence of pituitary gland, 803
Physicians: See Obituaries
Pierce, M.: Reports of Subcommittees of British Paediatric Association, 147
Pilcher, J. D.: Premenstrual state in young girls, *296
Pinworms: See Oxyuriasis
Pituitary Body, Cushing's syndrome in children; review of literature and report of case, *593
effect of estrogens, gonadotropins and growth hormone on mammary glands of hypophysectomized rats, 348
effect of thyroidectomy of young male goats on certain AP hormones, 349
hypophysial adamantinoma, 948
"mammogen" and treatment of spayed hypophysectomized rats with lipoid extracts of cattle pituitary, 185
secretion; does pregnancy suppress lactogenic hormone of pituitary? 187
site of elaboration of pituitary gonadotropic hormone and of prolactin, 347
studies of calcium and phosphorus metabolism; influence of pituitary gland, 803
Pituitary Preparations, assay of posterior pituitary factors which contract lactating mammary gland, 349
effect of administering thyrotropic hormone with and without iodine on thyroid tissue metabolism, 186
effect of increasing number of daily injections of gonadotropic preparations on ovaries of immature rats, 185
effect of pituitary growth substance on development of rats thyroidectomized at birth, 348
treatment of enuresis by means of injections of anterior pituitary extracts, 675
Placenta, ascorbic acid content of placenta, blood from umbilical vein and colostrum, 806
effect of depriving infant of its placental blood, 939
fibrinopenia in women with premature detachment of, 814
transfer of bismuth into fetal circulation after maternal administration of sobisminol, 940
Plague, so-called plague of Thucydides; interpretation and identification, 670
Plantain, use in infantile diarrhea, 804
Plants, oak poisoning; cause removing treatment, 189

Pleurisy, staphylococcus antitoxin in pleural exudates and spinal fluid, 810
Plumbism: See Lead poisoning
Pneumococci, pneumococcal meningitis; recovery, 346
pneumococcic sepsis and peritonitis in child suffering from nephrosis cured with sulfapyridine, 510
response of sulfapyridine-resistant pneumococci to hydroxyethylapocupreine, 328
sulfapyrazine (2-sulfanilamidopyrazine); its antipneumococcal activity as compared with that of sulfapyridine, sulfathiazole and sulfadiazine, 329
treatment of pneumococcic meningitis, 945
Pneumography: See Brain, roentgenography
Pneumonia: See also Bronchopneumonia
at Cook County Hospital, season of 1941, 342
cutaneous reactions with specific soluble substance (Francis test), 502
idiopathic cardiac enlargement occurring in infants and children, 174
pseudocaverns, 817
studies on vitamin A; vitamin A and total lipid of serum in pneumonia, *712
Tuberculosis: See Tuberculosis, pulmonary
Pneumothorax, neonatal, 332
with costal osteomyelitis in newborn infants, 665
Poisons and Poisoning: See under names of substances, as Bromide and Bromine; Food; Lead; Oak; etc.
Poliomyelitis: See also Encephalomyelitis
acute anterior, and Guillain-Barré syndrome ("infectious polyneuritis"), *431
acute anterior, differential diagnosis in, 334
acute; isolation of virus from case in Peiping with histopathologic studies, 491
anterior, second attacks of; report of 4 cases, *757
cardiac muscle in, *733
epidemiologic study in Mississippi in 1941, 489
high incidence of infective stools in small outbreak of infantile paralysis, 488
infantile paralysis, 334
Kenny treatment of infantile paralysis, 939
1937-1938 epidemic of acute anterior poliomyelitis in New South Wales, with reference to change in age incidence, poliomyelitis during pregnancy and poliomyelitis following tonsillectomy, 807
protection in white mice with human convalescent serum against infection with poliomyelitis virus (Armstrong strain), 335
virus hepatitis; contribution to knowledge of clinical picture of poliomyelitis and encephalitis, 819
Pollen: See Anaphylaxis and Allergy; Asthma
Polyarthritis: See Arthritis
Polyps: See Colon
Polyradiculoneuritis: See Nerves, roots
Polyuria: See Diabetes Insipidus
Postoloff, A. V.: Cushing's syndrome in children; review of literature and report of case, *593
Potassium, toxicity of orally administered potassium salts in renal insufficiency, 509
Pott's Disease: See Spine, tuberculosis
Pregnancy: See also Fetus; Labor; Maternity
calcium and phosphorus metabolism in osteomalacia; pathogenetic role of pregnancy and relative importance of calcium and vitamin D supply, 511
congenital malformations induced in rats by maternal nutritional deficiency; cleft palate, *882
dependence of fetal growth and storage of calcium and phosphorus on parathyroid function and diet of pregnant rats, 167
does pregnancy suppress lactogenic hormone of pituitary? 187
fibrinopenia in women with premature detachment of placenta, 814
influence on renal cortex of mice as indicated by structure of Bowman's capsule, 348
Pregnancy—Continued
Multiple: See Twins
1937-1938 epidemic of acute anterior poliomyelitis in New South Wales, with reference to change in age incidence, poliomyelitis during pregnancy and poliomyelitis following tonsillectomy, 807
prevention of hypoprothrombinemia in newborn infants by treating pregnant woman with vitamin K, 333
transfer of bismuth into fetal circulation after maternal administration of sobisminol, 940
Premature Infants, calcium and phosphorus requirements of, *412
calorie requirements of full-term and premature infants in neonatal period; formula; its uses and limitations, 487
causes of prematurity; influence of race and sex on duration of gestation and weight at birth, *523
growth of prematurely born children of school age, 665
infant mortality and prematurity, 665
pathology of, 938
premature death rate in clinic at Basel, 939
respiratory metabolism in infancy and in childhood; regulation of body temperature of premature infants, *376
values of plasma phosphatase and blood phosphorus in healthy children born at term and in premature children, 499
Presentation: See Labor
Pringle-Bourneville's Disease: See Sclerosis, tuberous
Prolactin: See Pituitary Body
Protamine Insulin: See under Diabetes Mellitus
Proteins: See also Amino Acids; etc.
dietary requirements for fertility and lactation, 937
in Blood: See Blood, proteins
in Cerebrospinal Fluid: See under Cerebrospinal Fluid
production of cytoplasmic inclusions in liver cells of rats injected with certain proteins, 190
stored protein in organism of infants and children; investigations to determine circulating reserve protein in blood plasma, 805
Prothrombin: See Blood, coagulation
Pruritus, familial occurrence of pruritus, urticaria and paresthesias with hyperkinesis of lower extremities, 823
Pseudohermaphroditism: See Hermaphroditism
Pseudoparalysis, Parrot's disease with icterus and umbilical hemorrhage, 670
Psittacosis, spontaneous ornithosis (psittacosis) in chickens cause of human infection, 494
Psychiatry: See Psychoanalysis; etc.
Psychoanalysis, important factor in eating disturbances of childhood, 346
psychoanalytic study of fraternal twin, 949
Psychoses: See Nervous and Mental Disabilities
Puberty: See Adolescence
Puericulture: See Child Welfare
Puerperium: See Labor; Lactation; Pregnancy
Purpura, Haemorrhagica: See also Blood, platelets; Diathesis, hemorrhagic
haemorrhagica; thrombocytopen; confirmatory report, 496
Thrombocytopenic; Thrombopenic: See Purpura, haemorrhagica
toxic reaction to sulfapyridine, 954
Pyelography: See also Kidneys
after subcutaneous injection of dye, 185
Pyemia: See under Bacteremia; Septicemia; Staphylococci; etc.
Pylorus, late results of operation for congenital pyloric stenosis, 820
Pyridoxine: See also Vitamins, B
Sydenham's chorea; preliminary report of 3 cases successfully treated with vitamin B_6, 178
vitamins E and B_6 in treatment of neuromuscular diseases, 945
Pyrimidine: See Urine, pyrimidine
Pyuria: See Urinary Tract, infections

Races: See also Negroes; etc.
causes of prematurity; influence of race and sex on duration of gestation and weight at birth, *523
Rachischisis: See Spina Bifida
Rachitis: See Rickets
Rack, F.: Independence of serum cholesterol from exogenous cholesterol in infants and in children, *235
Radiations: See under names of various diseases
Radiculitis: See Nerves, roots
Radio, children's reactions to movie horrors and radio crime, 182
Radiography: See Thorax
Radium, Therapy: See Hemangioma
Radius; congenital proximal radioulnar synostosis, 351
Rambar, A. C.: Studies in immunity to pertussis; effect of stimulating dose of Haemophilus pertussis vaccine, *730
Ramon Anatoxin: See under Diphtheria
Rat-Bite Fever, report of 2 cases; review of American reports from 1931 to 1940; observations on isolation of Spirillum minus, and results of standard serologic tests, 493
Ratner, Bret, appointment of, 326
Reading, ocular policy for public schools, 938
Recklinghausen's Disease: See Neurofibromatosis
Reflex, asthma reflex originating in tonsil, 672
developmental changes in attitude as 1 factor determining energy output in motor performance, 181
Religion, pediatric aspects of Salem witchcraft tragedy; lesson in mental health, *788
Reproduction: See also Pregnancy
dietary requirements for fertility and lactation, 937
effect of testosterone propionate in female, 186
Resins; oak poisoning; cause removing treatment, 189
Respiration, physiology and anatomy of respiratory system in fetus and newborn infant, 486
Respiratory Quotient: See Metabolism
Respiratory Tract: See also Nasopharynx; Nose; Pharynx; etc.
Diseases: See also Bronchitis; Pneumonia; etc.
diseases; acute laryngotracheal bronchitis; cure by endoscopic therapy, 814
diseases; effect of streptococcal upper respiratory infections on rheumatic children; 3 year study, 492
diseases; laryngotracheobronchitis, 341
method for studying expectorant action in animals by direct measurement of output of respiratory tract fluids, 342
open safety pin, 340
Reticuloendothelial System: See Anemia, splenic; Jaundice; Liver; Mononucleosis, Infectious; etc.
Reticulosarcoma, costovertebral, of Ewing in infant of 7 months, 676
Retina, hemorrhages in newborn, 330
retinal tuberous sclerosis (Bourneville's disease), 950
Retinitis punctata albescens, 822
Rhabdomyoma; tuberous sclerosis, 345
Rheumatic Fever, acute rheumatism and trauma, 173
changing heart murmurs of acute rheumatism, 173
effect of acetylsalicylic acid on sedimentation rate of erythrocytes in, 338
effect of streptococcal upper respiratory infections on rheumatic children; 3 year study, 492
epidemic of influenza B occurring in group of rheumatic children concurrent with outbreak of streptococcal pharyngitis; clinical and epidemiologic observations, 807
formol-gel test; comparison with sedimentation rate and Weltmann reaction, 172
nutrition as conditioning factor in rheumatic state, *744
Rheumatic Fever—Continued
occurrence of rheumatic disease with and without cardiopathies in hospital of Buenos Aires during year 1938, 494
prognosis in erythema annulare rheumaticum, 352
progress in rheumatic heart disease, 172
staphylococcic septicemia of rheumatic type, 669
Rheumatism: See Arthritis
Acute: See Rheumatic Fever
Ribs, abnormalities; earliest English example of bilateral cervical rib, 187
costal osteomyelitis with pneumothorax in newborn infant, 665
costovertebral reticulosarcoma of Ewing in infant of 7 months, 676
Rickets: See also Vitamins, D
and cod liver oil prophylaxis, 806
Celiac: See Celiac Disease
intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome); report of case in which increased urinary organic acids were detected and identified, with review of literature, *81
late, *314
Renal: See Dwarfism
studies on growth and development of male children receiving evaporated milk; effect of various vitamin supplements on growth in length and incidence of rickets during first 2 years of life, 168
three familial cases of atypical late vitamin-resistant rickets, 806
treatment and prophylaxis of rickets and infantile tetany with single giant dose of vitamin D_2, 330
Rickettsia: See also Typhus
hereditary transmission of Rickettsiae of tick bite fever through common dog tick, Haemaphysalis leachi, 173
Ripps, M. L.: Pseudoreactions to tuberculin, *763
Rodriguez, P. M.: Excretion of 17-keto steroids by normal and by abnormal children, *364
Roentgen Rays, Therapy: See Hemangioma; Tonsils
Rogatz, J. L.: Congenital defect of skin in newborn infant, *916
Rosen, A. N.: Congenital idiopathic cardiac hypertrophy, *905
Rosenthal Method: See under Tuberculosis
Roundworms: See Oxyuriasis
Rubeola: See Measles
Rubinstein, J. M.: Tumors of brain in children and in adolescents; clinical and anatomic survey of 92 verified cases, *604

Sachs-Tay Disease: See under Idiocy
St. Vitus' Dance: See Chorea
Salem, pediatric aspects of Salem witchcraft tragedy; lesson in mental health, *788
Salicyl Compounds, enzymatic debridement in local treatment of burns; preliminary report, *909
Saliva, rate of secretion of parotid glands in normal children; measurement of function of autonomic nervous system, *455
Salivary Gland: See also Parotid Gland; Submaxillary Gland
aberrant, in tonsillar fossa, 176
Salmonella: See also Food, poisoning
bacteriologic aspects of salmonellosis, 481
clinical aspects of salmonelloses, 495
Typhi Murium: See Food, poisoning
Salts, comparison between dehydration from salt loss and from water deprivation, 937
Sands, I. J.: Encephalitis complicating measles; report of 56 cases with follow-up studies in 32, *265
Sarcoidosis, effect of Schaumann's disease on heart and its mechanism, 943
Sarcoma: See also Reticulosarcoma; and under names of organs and regions
osteogenic, 351
Saturnism: See Lead poisoning
Scabies, treatment with benzyl benzoate; preliminary report, 514

Scalp, congenital defect of skin in newborn infant, *916
Scarlatina: See Scarlet Fever
Scarlet Fever: See also Streptococci
blood sedimentation tests in, 668
compulsory hospitalization of patients, 809
electrocardiographic examinations in, 809
erythrocytic sedimentation rate and Weltmann reaction in, 333
immunity following, 490
immunization, 333
recurrence of, 809
recurrent exanthem in course in 1,000 cases, 940
serous meningitis as complication of, 810
serous meningitis, ulcerative stomatitis and infectious arthritis with epiphysiolysis of left hip joint in, 491
Schaumann's Disease: See Sarcoidosis
Schick Test: See Diphtheria
Schönberg-Albers' Disease: See Osteosclerosis fragilis
Schonfeld, W. A.: Primary and secondary sexual characteristics; study of their development in males from birth through maturity, with biometric study of penis and testes, *535
Schools: See also Universities
democracy and popular school (Argentina), 486
Mantoux intradermal reaction in preschool and school age children in Villahermosa, 941
medical certificate for entrance to primary and secondary educational establishments (Bolivia), 486
ocular policy for public schools, 938
Schraffenberger, E.: Congenital malformations induced in rats by maternal nutritional deficiency; cleft palate, *882
Schüller-Christian Syndrome, multiple xanthomatosis tuberosa, 943
Schwarz, H.: Lipid nephrosis; observations over period of 20 years, *355
Sclera, blue, syndrome of; its presence in 5 generations, 677
corneoscleral cyst, 513
Sclerosis, amyotrophic lateral; vitamins E and B_6 in treatment of neuromuscular diseases, 945
disseminated, demonstration of myelolytic substances in, 179
tuberous, 345
tuberous, retinal (Bourneville's disease), 950
Scopolamine: See Anesthesia
Scorbutus: See Scurvy
Scrofulosis: See Tuberculosis
Scurvy: See also Ascorbic Acid
esophagospasm as cause of, 806
Secretions, Internal: See Endocrine Glands
Senility: See Old Age
Sensation, disorders; familial occurrence of pruritus, urticaria and paresthesias with hyperkinesis of lower extremities, 823
Sensitization: See under Anaphylaxis and Allergy; Immunity; etc.
Septicemia: See also under organisms and diseases, as Staphylococci; etc.
postanginal sepsis, 673
Septum, Nasal: See under Nose
Pellucidum: See Brain
Serum: See Blood
Convalescent: See under Communicable Diseases; Diphtheria; Measles; Meningitis; Pneumonia; Poliomyelitis; Scarlet Fever; Smallpox; Whooping Cough; etc.
Sex, causes of prematurity; influence of race and sex on duration of gestation and weight at birth, *523
education of adolescent, 508
Intergrades: See under Hermaphroditism
primary and secondary sexual characteristics; study of their development in males from birth through maturity, with biometric study of penis and testes, *535
Sheldon, W.: Dosage of vitamin D; opinions on vitamin D requirements of infants and children, 158
Shepherd, M. L.: Value of complex carbohydrates in diets of normal children, *195
Sherman, M.: Diagnosis of juvenile psychosis, *868
Shigella Dysenteriae: See Dysentery
Silver Picrate: See Gonorrhea
Sinuses, Nasal; otorhinogenic hydrocephalus, 345
sinusitis and Staphylococcus aureus bacteremia; recovery, 176
Size discrimination in children, 182
Skeleton: See Bones
Skin: See also Sensation
abnormalities: congenital defect in newborn infant, *916
abnormalities; syndrome of cutaneous fragility and hyperelasticity and articular hyperlaxity, *247
Diseases: See Dermatitis; and under names of diseases, as Eczema; etc.
Reactions: See Anaphylaxis and Allergy; etc.
transplantation by injection, 189
Skull: See Cranium
Slobody, L. B.: Symphalangism; familial malformation, *550
Smallpox, discussion on active immunization; some present-day problems, 337
Dr. J. N. Hell, physician of Sopron, introduces smallpox vaccination into Hungary, 668
estimations of thyroid hormone in infectious diseases, 490
history of inoculation before Edward Jenner, 491
postinfectious encephalomyelitis; report of its occurrence following measles and vaccination for smallpox, with complicating bromide poisoning, *585
so-called plague of Thucydides; interpretation and identification, 670
Smith, C. H.: Familial blood studies in cases of Mediterranean (Cooley's) anemia; diagnosis of trait, or mild form of disease, *681
Snuff: See Diphtheria
Societies, American Board of Pediatrics, 194, 326, 480, 825, 958
American Pediatric Society, meeting postponed, 480
foreign, directory of, 959
international, directory of, 959
local, directory of, 963
national, directory of, 960
pediatric, directory of, 959
sectional, directory of, 961
state, directory of, 961
Sodium Amytal: See Barbital and Barbital Derivatives
Diphenyl Hydantoinate: See Phenytoin
Sounds, perception; effect of noise on normal and impaired hearing, 816
Soybeans, determination of soybean milk used as adulterant in cow's milk, 170
Spasm: See Chorea; Convulsions; Epilepsy; etc.
Specimens, action of formaldehyde on nervous system, 180
Speech, cleft palate and mechanism of, 341
congenital auditory atresia; its plastic repair with functional restoration of hearing and phonation in deaf-mute, 673
Sperry, W. M.: Serum cholesterol values for infants and children, *858
Spina Bifida, enormous myelomeningocele with fatal leakage, 506
Spinal Cord: See also Nervous System; etc.
changes in Landry's paralysis, 675
transverse lesion following antitetanus serum therapy given intraspinally, 494
vascular malformations and vascular tumors involving spinal cord; pathologic study of 46 cases, 178
Spinal Fluid: See Cerebrospinal Fluid
Spine, costovertebral reticulosarcoma of Ewing in infant of 7 months, 676
tuberculosis; Pott's disease and sudden death in child of 4, 670
Spirochetosis, icterohemorrhagic; Weil's disease, 811
Spleen, Hypertrophy: See Splenomegaly

Splenectomy: See Anemia
Splenomegaly: See also Anemia, splenic
probable splenic portal thrombosis with roentgenographic study of esophageal varices, 944
Sports: See Athletics
Sprue, Nontropical: See Celiac Disease
Squint: See Strabismus
Stanard, R.: Studies in immunity to pertussis; effect of stimulating dose of Haemophilus pertussis vaccine, *730
Staphylococci, "coccic diphtheroids," further form of diphtheroid angina, 809
infection of submaxillary gland with fatal outcome, 344
periumbilical staphylococcus erysipelas in 20 day old infant, 488
presternal staphylococcic abscess complicating osteomyelitis, 676
septicemia and meningitis of staphylococcic origin, 668
sinusitis and Staphylococcus aureus bacteremia; recovery, 176
staphylococcic septicemia of rheumatic type, 669
staphylococcus antitoxin in pleural exudates and spinal fluid, 810
Starbuck, G. W.: Paroxysmal tachycardia in 2 month old infant with ventricular rate of 350, *582
Status Asthmaticus: See Asthma
Epilepticus: See Epilepsy
Steatorrhea: See Celiac Disease
Steinberg, M. F.: Newer concepts in diagnosis of congenital heart disease, *922
Steiner, M. M.: Diabetic coma, acute pancreatitis and Bacillus welchii peritonitis, *36
Sterilization of syringes and needles, 337
Sexual: See Castration
Sternum, Puncture: See Bones, marrow
Stethogram: See under Fetus
Stevens-Johnson Disease: See Erythema multiforme
Stilbestrol: See Estrogens
Stillbirths: See also Infant Mortality
high stillbirth and neonatal mortalities, 938
Stitt, P. G.: Postinfectious encephalomyelitis; report of its occurrence following measles and vaccination for smallpox, with complicating bromide poisoning, *585
Stomach: See also Gastrointestinal Tract; Pylorus; etc.
abnormalities; brachymegaesophagus with gastric displacement, 818
acid-base balance, renal function and gastric secretion during hypochloremia in dog, 803
effect of sodium amytal on emptying time of normal human stomach, 343
relation of nutrition to gastric function; effect of vitamin A dificiency, 503
relation of nutrition to gastric function; effect of vitamin B_1 deficiency, 484
Ulcer: See Peptic Ulcer
Stomatitis, aphthous, and nicotinic acid, 945
monocytic and myeloid-leukemoid reaction in severe fibrinous-necrotic stomatitis of child, 505
ulcerative, serous meningitis and infectious arthritis with epiphysiolysis of left hip joint in scarlet fever, 491
Vincent's: See Fusospirochetosis
Stools: See Feces
Strabismus, early treatment of squint, 188
functional, 952
functional, surgical treatment of, 677
Strassburger, P. J.: Guillain-Barré syndrome ("infectious polyneuritis") and acute anterior poliomyelitis, *431
Strean, L. P.: Attempts to enhance virulence of Haemophilus pertussis by serial passage in mice, *895
Streptococci: See also Scarlet Fever; etc.
"coccic diphtheroids," further form of diphtheroid angina, 809
effect of streptococcal upper respiratory infections on rheumatic children; 3 year study, 492
Streptococci—Continued
epidemic of influenza B occurring in group of rheumatic children concurrent with outbreak of streptococcal pharyngitis; clinical and epidemiologic observations, 807
mode of action of neoprontosil (azosulfamide) in streptococcus infections in mice, 173
streptococcic antifibrinolysin in newborn infants; true and false tests, *60
subacute bacterial endocarditis due to hemolytic streptococci of Lancefield group G, *77
Stuart, H. C.: Need for observations of growth in appraising adequacy of nutrition in childhood, *320
Submaxillary Gland, staphylococcus infection with fatal outcome, 344
Succinyl Sulfathiazole: See Sulfanilamide
Sugars: See Carbohydrates; Dextrose; Lactose; etc.
in Blood: See Blood, sugar
in Urine: See Diabetes Mellitus
Sulfadiazine: See Sulfanilamide and Sulfanilamide Derivatives
Sulfanilamide and Sulfanilamide Derivatives, acute hemolytic anemia from sulfonamides, 813
dosage interval in sulfapyridine administration, 955
effects of various urinary antiseptics on strains of Escherichia coli; sulfathiazole; urinary acidity, mandelic acid, methenamine and methenamine mandelate; relative value of sulfathiazole, sulfadiazine, sulfapyridine, sulfacetimide and sulfanilamide, *399
interstitial myocarditis in mice and rats produced by neoprontosil, sulfanilamide, sodium sulfapyridine and sodium sulfathiazole, 175
succinyl sulfathiazole, new bacteriostatic agent locally active in gastrointestinal tract, 177
sulfadiazine; review of its use in treatment of children, *702
sulfapyridine stone formation in urinary tract, 346
Therapy: See Burns; Diphtheria; Erysipelas; Meningitis; Otorhinolaryngology; Trachoma; etc.
toxic reaction to sulfapyridine, 954
Sulfapyridine: See Sulfanilamide and Sulfanilamide Derivatives
Sulfathiazole: See Diphtheria; Sulfanilamide and Sulfanilamide Derivatives
Sulfonamide: See Sulfanilamide and Sulfanilamide Derivatives
Suppositories: See Gonorrhea
Suprarenal Preparations: See Adrenal Preparations
Suprarenals: See Adrenals
Surgery: See also Apparatus; Instruments; Wounds; etc.
plastic; congenital auditory atresia; its plastic repair with functional restoration of hearing and phonation in deaf-mute, 673
Sussman, M. L.: Newer concepts in diagnosis of congenital heart disease, *922
Sympathectomy: See Colon, dilatation
Symphalangism: See Fingers and Toes
Synostosis: See Radius; Ulna
Syphilis: See also under names of organs and regions, as Ear; etc.
congenital, dental stigmas of, 940
congenital, incidence and prophylaxis, 174
congenital, prevention in large urban hospital; study of clinic administration, 339
congenital, roentgenographic diagnosis in unerupted permanent teeth, 941
Hereditary: See Syphilis, congenital
pseudosyphilitic bronchopneumonia (pulmonary infiltrations with positive Wassermann reactions), 502
relation of changes in testicular structure induced in rabbit by estrogenic substance to resistance against syphilis, 348
syphilitic mediastinitis in infant of 2 months, 672
Syringes, sterilization of syringes and needles, 337

Tachycardia: See Arrhythmia
Talbot, N. B.: Excretion of 17-keto steroids by normal and by abnormal children, *364
Tannic Acid: See Burns
Tat, R. J.: Erythroblastosis foetalis (acute hemolytic anemia of newborn); preliminary report, *571
Output of bile pigment by newborn infants and by older infants and children, *558
Tay-Sachs Disease: See under Idiocy
Taylor, C. E.: Waterhouse-Friderichsen syndrome on Isthmus of Panama, *426
Teeth, dental stigmas of congenital syphilis, 940
influence of formative dental organs on growth of bones of face, 954
principles of skeletal growth, 954
roentgenographic diagnosis of congenital syphilis in unerupted permanent teeth, 941
Telangiectasis: See also Angioma
hereditary hemorrhagic, with gastrointestinal bleeding, 503
multiple hereditary hemorrhagic, 353
Tellurite Reaction: See Diphtheria
Temperature: See also Fever; Heat; etc.
respiratory metabolism in infancy and in childhood; regulation of body temperature of premature infants, *376
Temporal Bone, abscess of mandibular fossa secondary to otitis media, 176
Testes, effect of large amounts of androgen on testes of prepuberal rat, 186
Internal Secretion of: See Androgens; etc.
primary and secondary sexual characteristics; study of their development in males from birth through maturity, with biometric study of penis and testes, *535
relation of changes in testicular structure induced in rabbit by estrogenic substance to resistance against syphilis, 348
Testosterone: See Androgens
Tetanus, discussion on active immunization; some present-day problems, 337
immunity against diphtheria and tetanus in animals, 489
immunity induced by third dose of toxoid 2 years after basic immunization, based on study of 31 allergic children, *873
otogenous, 810
sensitization induced by tetanus toxoid, alum precipitated, 492
transverse lesion of spinal cord following antitetanus serum therapy given intraspinally, 494
treatment, 337
Tetany, cause of edema in, 506
genuine tetanic nutritional cataract, 953
infantile; treatment with dihydrotachysterol (A. T. 10), 180
treatment and prophylaxis of rickets and infantile tetany with single giant dose of vitamin D_2, 330
Thaysen-Gee Disease: See Celiac Disease
Thiamine: See also Beriberi; Vitamins, B
and pyrimidine studies on older subjects, 330
effects of vitamins B_1 and C on endocrine equilibrium in infancy, 805
influence of minor dietary changes on frequency of infants' stools; study of effect of varying content of lactose, milk fat and thiamine, *827
relation of nutrition to gastric function; effect of vitamin B_1 deficiency, 484
Wernicke's encephalopathy; clinical features and their probable relationship to vitamin B deficiency, 506
Thirst, breast milk secretion during thirst and during forced fluid intake, 805
Thomas, E. M.: Total and fractional blood lipid levels in nephrotic syndrome, *770
Thorax: See also Heart; Lungs; Mediastinum; Ribs; etc.
mass radiography of chest, 176
presternal staphylococcic abscess complicating osteomyelitis, 676
Threadworms: See Oxyuriasis
Throat: See also Larynx; Pharynx; Tonsils; etc.
aberrant salivary gland in tonsillar fossa, 176
Thrombin: See Blood, coagulation
Thrombocytopen: See Purpura, haemorrhagica
Thrombopenia: See under Purpura, haemorrhagica
Thrombosis and coronary calcification in infant, 175
probable splenic portal thrombosis with roentgenographic study of esophageal varices, 944
Thucydides, so-called plague of Thucydides; interpretation and identification, 670
Thumb: See Fingers and Toes
Thyroid: See also Parathyroid
effect of administering thyrotropic hormone with and without iodine on thyroid tissue metabolism, 186
effect of pituitary growth substance on development of rats thyroidectomized at birth, 348
effect of thyroidectomy of young male goats on certain AP hormones, 349
Hormone: See Thyroxin
hyperthyroidism, 821
hyperthyroidism; effect of testosterone propionate on creatinuria of experimental hyperthyroidism in male and female monkeys, 186
hyperthyroidism; radiotherapy in thyrotoxicosis, 350
hyperthyroidism; vitamin K in other than hemorrhagic diseases, 339
Hypothyroidism: See also Cretinism
hypothyroidism; excretion of 17-keto steroids by normal and by abnormal children, *364
relation between thyroid function and cholesterol content of blood of infants and larger children, 821
Thyroidectomy: See under Thyroid
Thyrotoxicosis: See Thyroid, hyperthyroidism
Thyroxin, estimations of thyroid hormone in infectious diseases, 490
Tick Fevers: See also Typhus
hereditary transmission of Rickettsiae of tick bite fever through common dog tick, Haemaphysalis leachi, 173
Tissue: See Cells
Adipose: See Fat; Obesity
Tocopherol: See Vitamins, E
Toes: See Fingers and Toes
Tonsillectomy in cases of peritonsillar abscess, 501
in children, 815
influence on blood picture, 815
1937-1938 epidemic of acute anterior poliomyelitis in New South Wales, with reference to change in age incidence, poliomyelitis during pregnancy and poliomyelitis following tonsillectomy, 807
postoperative hemorrhages from tonsils and adenoids, 673
Tonsillitis: See Tonsils
Tonsils, asthma reflex originating in tonsil, 672
modern treatment of acute tonsillitis by injections of bismuth compounds, 340
postanginal sepsis, 673
roentgen therapy for chronic infections of lymphoid ring of Waldeyer, 944
Toxin and Antitoxin: See under Diphtheria; Scarlet Fever; Staphylococci; Tetanus; Whooping Cough; etc.
Toxoid: See under Diphtheria; Tetanus; etc.
Trachea, hernia; tracheocele; report of case, 672
tracheobronchitis complicating grip and its treatment, 817
Tracheocele: See Trachea, hernia
Tracheotomy and intubation for diphtheritic croup, 667
Trachoma and sulfanilamide, 822
Tracy, P. C.: Diabetic coma, acute pancreatitis and Bacillus welchii peritonitis, *36
Transfusion: See Blood, transfusion
Transplantation: See under Skin
Tuberculin: See also Tuberculosis
pseudoreactions to, *763

Tuberculosis: See also under names of organs, regions and diseases, as Eyes; Kidneys; Spine; etc.
allergy studies on tuberculous eyes, 512
and heredity, 812
antituberculous prophylaxis, 173
athletic activity at puberty with reference to cardiac and tuberculous patient, 498
Calmette vaccination of young persons, 812
interval between renal tuberculosis and initial tuberculosis, 671
Mantoux intradermal reaction in preschool and school age children in Villahermosa, 941
percutaneous (Rosenthal) method of BCG vaccination, 812
possible significant errors in routine tuberculin tests, 495
primary tuberculous infection in infancy, 812
pseudoreactions to tuberculin, *763
pulmonary; Loeffler's syndrome, 674
pulmonary; Weltmann's coagulation reaction in serum in pulmonary and in extrapulmonary tuberculosis, 495
scrofulosis in childhood; historical review from Hippocrates to present time, 670
state of allergy exhibited by tuberculous children in Gothenburg with reference to Gröer's allergometric method, 671
studies in; relative incidence of human and bovine types of Mycobacterium tuberculosis in human disease in Victoria, 174
two phases of development, 339
Tuchewicz, H.: Premenstrual state in young girls, *296
Tudor, R. B.: Stones in urinary bladder in children; diagnosis and treatment in 7 cases, *591
Tularemia caused by insect bite, 670
Tumors: See Adamantinoma; Angioma; Chloroma; Chordoma; Diktyoma; Hemangioma; Myeloma; Phacoma; Rhabdomyoma; Sarcoma; and under names of organs and regions, as Adrenals; Brain; Heart; etc.
Twins, psychoanalytic study of fraternal twin, 949
Typhoid and paratyphoid in nurslings, 669
in infants of 15 and 18 months, 669
peritonitis due to perforation of biliary vesicle in course of typhoid fever accompanied by suppurative parotitis, 811
vaccine, investigation on protective antibodies produced by oral administration of, 492
Typhus, so-called plague of Thucydides; interpretation and identification, 670

Ulcers: See under names of organs and regions
Peptic: See Peptic Ulcer
Ulna, congenital proximal radioulnar synostosis, 351
Ultraviolet Rays: See under names of organs and diseases
Umbilical Cord, ascorbic acid content of placenta, blood from umbilical vein and colostrum, 806
cure of congenital aplastic anemia (Benjamin type), 499
human cord serum globulin in modification and prevention of measles, 334
transfer of bismuth into fetal circulation after maternal administration of sobisminol, 940
Umbilicus, Fistula: See Fistula
Hernia: See Hernia, umbilical
Parrot's disease with icterus and umbilical hemorrhage, 670
periumbilical staphylococcus erysipelas in 20 day old infant, 488
persisting vitelline remnants (umbilical cyst and Meckel's diverticulum), 344
Universities, incidence of heart disease in university student age group, 942
Urea, relation of high and low urea clearances to inulin and creatinine clearances in children with nephrotic syndrome, 949
Ureters: See also Urinary Tract
obstruction; studies in experimental hypertension, 174
Urinary Tract: See also Genitals; Kidneys; Ureters; etc.
calculi; sulfapyridine stone formation in urinary tract, 346
diseases; urologic aspects of enuresis, 184
effects of various urinary antiseptics on strains of Escherichia coli; sulfathiazole; urinary acidity, mandelic acid, methenamine and methenamine mandelate; relative value of sulfathiazole, sulfadiazine, sulfapyridine, sulfacetimide and sulfanilamide, *399
infections, chronic, in children, 184
infections; pyuria, 184
Urination, incontinence; enuresis, 510
incontinence; enuresis of allergic origin; report of 2 cases, 185
incontinence; treatment of enuresis by means of injections of anterior pituitary extracts, 675
incontinence; urologic aspects of enuresis, 184
Urine: See also Urination; and under names of diseases; etc.
creatine and creatinine; effect of testosterone propionate on creatinuria of experimental hyperthyroidism in male and female monkeys, 186
demonstration of myelolytic substances in disseminated sclerosis, 179
intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome); report of case in which increased urinary organic acids were detected and identified, with review of literature, *81
levulosuric diabetes, 676
pyrimidine; thiamine and pyrimidine studies on older subjects, 330
steroids; excretion of 17-keto steroids by normal and by abnormal children, *364
Urography: See Pyelography
Urticaria, familial occurrence of pruritus, urticaria and paresthesias with hyperkinesis of lower extremities, 823
Uterus, attempts to induce menstruation by operative ischemia in monkeys, 183
uterine distention and lactation, 183
Uvea, diktyoma of ciliary body, 953

Vaccination: See Immunity; and under names of various diseases, as Smallpox; Typhoid; etc.
Encephalitis Following: See under Encephalitis
Vaccine: See Whooping Cough
Vaccinia: See Smallpox
Vagina, premenstrual state in young girls, *296
Vaginitis: See Gonorrhea
Varicella: See Chickenpox
Variola: See Smallpox
Vegetables: See Fruits and Vegetables
Venereal Diseases: See Gonorrhea; Syphilis
Ventriculography: See under Brain, roentgenography
Vertebrae: See Spine
Vestibular Apparatus: See Ear
Viruses: See also Influenza; Measles; Poliomyelitis; Psittacosis; etc.
neurotropic virus diseases of man, 493
Vision: See also Blindness; Eyes; etc.
tests; ocular policy for public schools, 938
Vital Statistics: See Infant Mortality
Vitamins: See also Diet and Dietetics; Food; Milk; Rickets; etc.
A: See also Carotene; Cod Liver Oil; Xerophthalmia
A, and total lipid of serum in pneumonia, *712
A; relation of nutrition to gastric function; effect of vitamin A deficiency, 503
A supply of Finnish people, 805
B: See also Beriberi; Nicotinic Acid; Pyridoxine; Thiamine
B; influence of inositol and other B complex factors on motility of gastrointestinal tract, 329

Vitamins—Continued
B_1: See Thiamine
B_6: See Pyridoxine
C: See Ascorbic Acid
D: See also Cod Liver Oil; Rickets
D; calcium and phosphorus metabolism in osteomalacia; pathogenetic role of pregnancy and relative importance of calcium and vitamin D supply, 511
D, dosage; opinions on vitamin D requirements of infants and children, 158
D; renal excretion of inorganic phosphate in relation to action of vitamin D and parathyroid hormone, 484
D; treatment and prophylaxis of rickets and infantile tetany with single giant dose of vitamin D_3, 330
Deficiency: See Beriberi; Deficiency Diseases; Rickets; Scurvy; etc.; and under specific vitamins
E: See also Reproduction
E and B_6 in treatment of neuromuscular diseases, 945
K: See also Blood, coagulation
K avitaminosis as cause of hemorrhagic diathesis in newborn and older infants, 332
K; blood prothrombin in newborn, 331
K in other than hemorrhagic diseases, 339
K; infarction of liver and hypoprothrombinemia; report of their association in newborn infant with failure of vitamin K therapy, *258
K; prevention of hypoprothrombinemia in newborn infants by treating pregnant woman with vitamin K, 333
K; prothrombin in newborn infant; further observations on prothrombin response to intravenous administration of water-soluble naphthoquinone, 487
studies on growth and development of male children receiving evaporated milk; effect of various vitamin supplements on growth in length and incidence of rickets during first 2 years of life, 168
three familial cases of atypical late vitamin-resistant rickets, 806
Vitelline Duct, congenital umbilical fistula or sinus due to persistent omphalomesenteric duct, 505
persisting vitelline remnants (umbilical cyst and Meckel's diverticulum), 344
Vitiligo, Addison's disease, creatine metabolism, 676
Vollmer, H.: Pseudoreactions to tuberculin, *763
Vollmer Patch Test: See Tuberculosis
Volvulus: See Intestines
Vomiting caused by anomaly of duodenum, 818
from postoperative inflammatory reaction in infancy, 817
intermittent, following constriction of duodenum by mesenteric pedicle, 818
Vulvovaginitis, Gonorrheal: See Gonorrhea

Wagner, R.: Galactose tolerance test in endocrine disorders in children, *207
Waldeyer Ring: See Tonsils
Warkany, J.: Congenital malformations induced in rats by maternal nutritional deficiency; cleft palate, *882
Wassermann Reaction: See Syphilis
Water: See also Fluids
comparison between dehydration from salt loss and from water deprivation, 937
Metabolism: See Dehydration; Edema
Waterhouse-Friderichsen Syndrome: See Adrenals, hemorrhage
Weaning: See Infant Feeding
Weech, A. A.: Basal heat production in relation to growth; longitudinal study on normal infants 6 to 20 months of age, *1
Weight: See Body, weight; Obesity
Weiner, H.: Syndrome of cutaneous fragility and hyperelasticity and articular hyperlaxity, *247
Weiner, S. B.: Lipid nephrosis; observations over period of 20 years, *355
Weltmann Reaction: See Blood, coagulation
Wernicke's Disease: See Encephalitis, hemorrhagic
Wheal: See Urticaria
Wheat Germ Oil: See Vitamins, E
Whooping Cough, active immunization in experimental pertussis, 336
attempts to enhance virulence of Haemophilus pertussis by serial passage in mice, *895
changes in brain in pertussis with convulsions, 333
clinical studies in immunity to pertussis with use of pertussis skin testing toxin and anti-endotoxin, 488
discussion on active immunization; some present-day problems, 337
influence of high altitude flights, 491
studies in immunity to pertussis; effect of stimulating dose of Haemophilus pertussis vaccine, *730
Winters, K. J.: Sulfadiazine; review of its use in treatment of children, *702
Witchcraft, pediatric aspects of Salem witchcraft tragedy; lesson in mental health, *788
Wolman, I. J.: Influence of minor dietary changes on frequency of infants' stools; study of effect of varying content of lactose, milk fat and thiamine, *827
Work, breast feeding in relation to female labor as it affects Birmingham, 147
Wounds, therapy; skin transplantation by injection, 189

Xanthomatosis: See Schüller-Christian Syndrome
Xeroderma pigmentosum; case report, 352
Xerophthalmia, Bitot's spots in Trinidad, 951

Zucker, J. M.: Tumors of brain in children and in adolescents; clinical and anatomic survey of 92 verified cases, *604

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CONTENTS

PAGE

Influence of Minor Dietary Changes on Frequency of Infants' Stools: Study of the Effect of Varying the Content of Lactose, Milk Fat and Thiamine. Irving J. Wolman, M.D., and Sydney Borowsky, M.D., Philadelphia 827

Basal Metabolism of Normal Boys and Girls from Two to Twelve Years Old, Inclusive: Report of a Further Study. Robert C. Lewis, Ph.D.; Anna Marie Duval, Ph.D., and Alberta Iliff, Ph.D., Denver 834

Basal Metabolism of Normal Children from Thirteen to Fifteen Years Old, Inclusive. Robert C. Lewis, Ph.D.; Anna Marie Duval, Ph.D., and Alberta Iliff, Ph.D., Denver 845

Serum Cholesterol Values for Infants and Children. Lieutenant Richard G. Hodges, Medical Corps, Army of the United States, and Warren M. Sperry, Ph.D., and Dorothy H. Andersen, M.D., New York 858

Diagnosis of Juvenile Psychosis. Mandel Sherman, M.D., and Hudson Jost, Ph.D., Chicago 868

Immunity to Tetanus Induced by a Third Dose of Toxoid Two Years After Basic Immunization Based on a Study of Thirty-One Allergic Children. M. Murray Peshkin, M.D., New York 873

Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency: IV. Cleft Palate. Josef Warkany, M.D.; Rose C. Nelson, Ph.D., and Elizabeth Schraffenberger, A.B., Cincinnati 882

Attempts to Enhance Virulence of Hæmophilus Pertussis by Serial Passage in Mice. Lyon P. Strean, Ph.D., D.D.S., Montreal, Canada 895

Electroencephalography on Children. Niels L. Low, M.D., Milwaukee 898

Congenital Idiopathic Cardiac Hypertrophy. A. Nathaniel Rosen, M.D., Brooklyn 905

Enzymatic Débridement in the Local Treatment of Burns: A Preliminary Report. Gerald R. Cooper, Ph.D.; G. B. Hodge, M.D., and J. W. Beard, M.D., Durham, N. C. 909

Case Reports:

Bacillus Pyocyaneus Meningitis Following Pneumoencephalography. W. Z. Kerman, M.D.; M. A. Perlstein, M.D., and A. Levinson, M.D., Chicago 912

Congenital Defect of the Skin in a Newborn Infant. Julian L. Rogatz, M.D., and Harold B. Davidson, M.D., New York 916

Large Cyst of the Omentum: Its Occurrence in a Three Year Old Child. William Leach, M.D., Shenandoah, Pa., and Mark Holland, M.D., Mahanoy City, Pa. 920

Progress in Pediatrics:

Newer Concepts in the Diagnosis of Congenital Heart Disease. Marcy L. Sussman, M.D.; Arthur Grishman, M.D., and Morris F. Steinberg, M.D., New York 922

Abstracts from Current Literature 937

Book Reviews 956

News and Comment 958

Directory of Pediatric Societies 959

General Index 967